UNITED STATES PATENT AND TRADEMARK OFFICE

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SEP 21 2006

Office of Regulatory Policy
HFD-7
5600 Fishers Lane (Rockwall II Rm 1101)
Rockville, MD 20857

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 5,061,703 was filed on December 9, 2003, under 35 U.S.C. § 156. It is noted that another patent term extension for U.S. Patent No. 5,614,560 was filed for the same product for the same regulatory review period as per 37 C.F.R. 1.785(b).

The assistance of your Office is requested in confirming that the product identified in the application, NAMENDA® (memantine hydrocholoride), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Adda C. Gogoris, Esq.
Darby &Darby, P.C.
805 Third Avenue
New York, NY 10022

COURTESY COPY

EXPRESS MAIL CERTIFICATE

Date _____ Label No. _____
I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to Mail Stop Patent Ext., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 by "Express Mail Post Office to Addressee" service.

Name (Print) _____ Signature _____

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Customer No.: 07278

Docket No.: 03269/8200177-000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,061,703

Inventors: Joachim BORMANN, Markus GOLD, and Wolfgang SCHATTON

Assignee: Merz Pharma GmbH & Co. KGaA

Title: ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

Issue Date: October 29, 1991

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

December 9, 2003

Mail Stop Patent Ext.
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Forest Laboratories, Inc. ("Forest") acting as agent of the patent owner Merz Pharma GmbH & Co. KGaA ("Merz") hereby requests an extension of the term of U.S. Patent No. 5,061,703 ("the '703 patent") pursuant to 35 U.S.C. § 156. The assignments for the '703 patent from the inventors to Merz are recorded at reel 005302, frame 0141 (recorded May 7, 1990); reel 012865,

frame 0219 (recorded May 1, 2002); and reel 013372, frame 0354 (recorded October 9, 2002). Copies of the recorded assignments are attached as Exhibit A. Also, a letter from an officer of Merz confirming that Forest is the sole exclusive licensee of the '703 patent and that Forest is authorized to act on behalf of Merz before the U.S. Patent and Trademark Office in connection with this Request is attached as Exhibit B. A Power of Attorney executed by an officer of Forest is attached as Exhibit C.

A total of five copies of this Request are submitted in compliance with 37 C.F.R. § 1.740(b) and as suggested by MPEP § 2753.

As permitted by 37 C.F.R. § 1.785(b) and MPEP § 2761, Forest is concurrently filing a request for patent term extension of U.S. Patent No. 5,614,560 based upon the same regulatory review period.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and follows the numerical format set forth in 37 C.F.R. § 1.740(a):

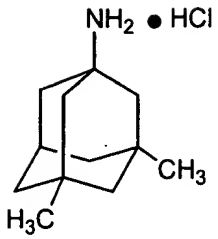
(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product will be marketed under the trademark NAMENDA™ in 5 mg, 10 mg, 15 mg, and 20 mg tablets for the treatment of moderate to severe dementia of the Alzheimer's type. The active ingredient of NAMENDA™ has

(a) the chemical name of 1-amino-3,5-dimethyladamantane hydrochloride;

(b) the generic name of memantine hydrochloride;

(c) the structural formula of:



(d) the empirical formula of $C_{12}H_{21}N \bullet HCl$; and

(e) a molecular weight of 215.76.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred under Section 505(b) of the Federal Food, Drug and Cosmetic Act (FFDCA), which is codified at 21 U.S.C. § 355(b). Section 505(b) (21 U.S.C. § 355(b)) provides for the submission and approval of New Drug Applications (NDAs).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

Memantine hydrochloride (NAMENDA™) received permission for commercial marketing from the Food and Drug Administration (FDA) pursuant to Section 505(b) of the FFDCA (21 U.S.C. § 355(b)) on October 16, 2003. A copy of the letter from the FDA approving marketing of memantine hydrochloride is attached as Exhibit D.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public

Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in the approved product is memantine hydrochloride. Memantine hydrochloride was not previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act prior to the approval referenced herein on October 16, 2003.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

Memantine hydrochloride (NAMENDA™) was approved for commercial marketing on October 16, 2003. The sixty day period expires on Monday, December 15, 2003. The present application, therefore, is timely filed within the sixty day period.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

Inventors: Joachim BORMANN, Markus GOLD, and Wolfgang SCHATTON

Patent No.: 5,061,703

Issue Date: October 29, 1991

Expiration Date: April 11, 2010

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the '703 patent is attached as Exhibit E.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

No disclaimers, certificates of correction, or reexamination certificates have been submitted or issued for the '703 patent.

The 3½ year, 7½ year, and 11½ year maintenance fees for the '703 patent have been timely paid. Copies of the receipts showing payment of the 3½ year, 7½ year, and 11½ year maintenance fees are attached as Exhibit F.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product;

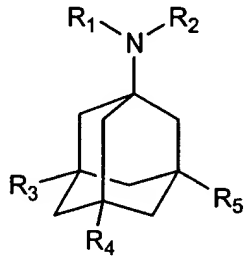
(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.

Claim 10 of the '703 patent is explicitly directed to treatment of Alzheimer's disease, a method for using the approved product, NAMENDA™ (memantine hydrochloride), referring to claim

1 for the generic formula which includes the approved active ingredient as explained infra. Claim 1 also covers a method of using the approved product in a generic manner. Claim 10 and the independent claim from which it depends (claim 1) are reproduced below:

> 10. A method according to claim 1 for the treatment of Alzheimer's disease.
>
> 1. A method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof, an effective amount of an adamantane derivative of the general formula



> wherein
>
> **R_1 and R_2 are identical** or different and represent **hydrogen** or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;
>
> wherein
>
> R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;
>
> wherein
>
> R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group,
>
> **or a pharmaceutically-acceptable salt thereof.**

The adamantane derivative of the general formula shown in claim 1 represents memantine hydrochloride when: R^1 and R^2 are hydrogen; one of R^3, R^4, and R^5 is hydrogen and the remaining two of R^3, R^4, and R^5 are methyl; and the pharmaceutically acceptable salt is the hydrochloride salt (see, '703, col. 4: 32-37).

Additional claims that cover a method for using the approved product include claims 2, 3, 6, 8, and 11-13.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) application or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

(ii) For a patent claiming a new animal drug ...

(iii) For a patent claiming a veterinary biological product ...

(iv) For a patent claiming a food or color additive ...

(v) For a patent claiming a medical device ...

The investigational new drug (IND) application for memantine hydrochloride (NAMENDA™) is IND application no. 33,392. Merz filed the IND application on July 10, 1989 (Exhibit G). The IND was placed on clinical hold within thirty days of its filing pursuant to 21 U.S.C. § 355(i)(3). The IND was inactivated on January 13, 1994 (Exhibit H). Merz filed a request for re-activation of the IND on September 5, 1997 (Exhibit I). The IND became effective on October 9, 1997 (Exhibit I), i.e., the exemption under 21 U.S.C. § 355(i) became effective thirty days after receipt of the request for re-activation by the FDA pursuant to 21 U.S.C. § 355(i)(2).

The NDA for memantine hydrochloride (NAMENDA™), NDA 21-487, was initially submitted to the FDA on December 19, 2002 (Exhibit L).

NDA 21-487 was approved by the FDA on October 16, 2003 (Exhibit D).

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

Merz, the owner of the '703 patent, submitted an IND application for NAMENDA™ on July 10, 1989 (Exhibit G). The IND (No. 33,392) was placed on clinical hold pursuant to 21 U.S.C. § 355(i)(3), and inactivated on January 13, 1994 (Exhibit H). *See* the Chronology of Regulatory Review of NAMENDA™ attached as Exhibit J.

21 U.S.C. § 355(i)(2) provides that clinical investigation of a drug may begin thirty days after receipt of the IND application by the FDA. On September 5, 1997, Merz filed a request for re-activation of the IND (Exhibit I). The IND became effective on October 9, 1997 (Exhibit I), thirty days after the FDA received the re-activation request from Merz. *See* 21 U.S.C. § 355(i)(2).

After the re-activated IND became effective, Merz promptly began its investigation of NAMENDA™. The studies referenced in the IND were begun and the FDA was notified of Protocol Amendments and amendments to the chemistry, Manufacturing and Control Sections and Pharmacology Sections of the IND. Merz also submitted the required information about investigators, and the required 15-day alert reports. On September 13, 2000, Merz transferred ownership of the IND to Forest (Exhibit K). Various conferences were held by Merz and Forest during the pendency of the re-activated IND in an effort to advance the regulatory review.

On December 19, 2002 Forest submitted an NDA for NAMENDA™, which was assigned number 21-487. A copy of the December 19, 2002 cover letter for the NDA is attached as Exhibit L. Forest promptly complied with all FDA requests for information during the NDA review (see the list of submissions to the FDA acknowledged in the FDA Approval Letter for NAMENDA™, attached as Exhibit D). The NDA was approved on October 16, 2003.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of the extension was determined.

It is the opinion of the applicant that the '703 patent is eligible for patent term extension under 35 U.S.C. § 156(a). The applicant claims an extension of 1250 days.

Statement of Eligibility of the Patent for Extension

Under 35 U.S.C. § 156(a)

Section 156(a) provides in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. § 156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 U.S.C. § 156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) except for 35 U.S.C. §§ 156(a)(5)(B) and 156(a)(5)(C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

Each of these elements is satisfied here:

(1) The term of the '703 patent expires on April 11, 2010. This application has, therefore, been submitted before the expiration of the patent term.

(2) The term of the '703 patent has never been extended.

(3) The application is submitted by Adda C. Gogoris, an attorney for Forest, which is the sole exclusive licensee of the '703 patent from the patent owner Merz. This application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning October 16, 2003 when the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. §§ 156(d)(1)(A)-(E).

(4) The product was the subject of an IND (filed on July 10, 1989; placed on clinical hold; inactivated on January 13, 1994; re-activated on September 5, 1997; and effective on October 9, 1997), and an NDA (filed on December 19, 2002 and approved on October 16, 2003). Thus, the product was subject to a regulatory review period under § 505(b) of the FFDCA before its commercial marketing or use.

(5) Finally, the permission for the commercial marketing of NAMENDA™ after regulatory review under FFDCA § 505(b) is the first permitted commercial marketing of NAMENDA™ in the United States. This is confirmed by the absence of any approved NDA under which NAMENDA™ could be commercially marketed prior to October 16, 2003.

Statement as to the Length of the Extension Claimed

In Accordance with 37 C.F.R. 1.775

The term of the '703 patent should be extended by 1250 days. The extension was determined according to 37 C.F.R. § 1.775 and the PTO worksheet "Calculation of Length for Patent Term Extension for a Human Drug Product" as follows:

(1)	1897	The number of days in: the period beginning on the effective date of the IND (October 9, 1997) and ending on the date the NDA was initially submitted (December 19, 2002). This is the "testing phase" as defined in 37 C.F.R. § 1.775(c)(1).

(2)	301	The number of days in the period beginning on the date the NDA was initially submitted (December 19, 2002) and ending on the date of NDA approval (October 16, 2003). This is the "approval phase" as defined in 37 C.F.R. § 1.775(c)(2).
(3)	2198	The sum of (1) and (2). This is the regulatory review period as define in 37 C.F.R. § 1.775(c).
(4)	0	The number of days in the approval phase (2) which were on and before issuance of the '703 patent. 37 C.F.R. § 1.775(d)(1)(i).
(5)	0	The number of days in the approval phase (2) during which the Applicant did not act with due dilligence. 37 C.F.R. § 1.775(d)(1)(ii).
(6)	0	The sum of (4) and (5).
(7)	2198	The difference between the regulatory review period (3) and (6). 37 C.F.R. § 1.775(d)(1)(ii).
(8)	0	The number of days of the period of the testing phase (1) which occurred prior to the issuance of the '703 patent. 37 C.F.R. § 1.775(d)(1)(i).
(9)	0	The number of days of the period of the testing phase (1) during which the Applicant failed to act with due dilligence 37 C.F.R. § 1.775(d)(1)(ii).
(10)	0	The sum of (8) and (9).
(11)	2198	The difference between the regulatory review period (7) and (10).
(12)	1897	The number of days of the testing phase (1).
(13)	0	The number of days from (10).
(14)	1897	Subtract line (13) from line (12)
(15)	948	One half of (14) 37 C.F.R. § 1.775(d)(1)(iii)[1]
(16)	1250	Subtract line (15) from line (11)
(17)	April 11, 2010	The original expiration date of the '703 patent.
(18)	Sept. 12, 2013	The expiration date of the '703 patent if the original expiration date is extended by the number of days in line (16). 37 C.F.R. § 1.775(d)(2)
(19)	Oct. 16, 2003	The date of approval of the application under § 505(b) of the FFDCA.

[1] 37 C.F.R. § 1.775(d)(1) provides that for purposes of subtraction, half days are ignored.

(20)	14 years	The limitation of 37 C.F.R. § 1.775(d)(3).
(21)	Oct. 16, 2017	The number of years in (20) plus the date on (19). 37 C.F.R. § 1.775(d)(3).
(22)	Sept. 12, 2013	The earlier of line (18) or line (21)
(23)	April 11, 2010	The original expiration date of the '703 patent.
(24)	5 years	The applicable limitation of 37 C.F.R. § 1.775(d)(5)
(25)	April 11, 2015	The number of years on (24) plus the date on (23).
(26)	Sept. 12, 2013	The earlier of line (22) or line 25
(27)	April 11, 2010	The original expiration date of the '703 patent
(28)	1250	The number of days which is the difference between the date on line (27) and the date on line 26

(13) A statement that the Applicant acknowledges a duty to disclose to the Commission of Patents and Trademarks and to the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought for the '703 patent by this Request as required by 37 C.F.R. § 1.765.

(14) Prescribed Fee:

A check in the amount of $1,120.00 required under 37 C.F.R. § 1.20(j) is enclosed with this Request. The Commissioner is authorized to charge any additional fees to Darby & Darby P.C., Deposit Account No. 04-0100.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

Adda C. Gogoris, Esq.
Darby & Darby, P.C.
805 Third Avenue
New York, NY 10022
Tel: (212) 527-7700
Fax: (212) 753-6237

In view of the foregoing, Forest, acting as agent for the patent owner Merz, requests that the Commissioner grant an extension of 1250 days to U.S. Patent No. 5,061,703.

Favorable action is earnestly solicited.

Respectfully submitted,

Adda C. Gogoris
Reg. No. 29,714
Attorney for Applicant

DARBY & DARBY P.C.
Post Office Box 5257
New York, NY 10150-5257
212-527-7700

REQUEST FOR EXTENSION OF PATENT TERM FOR U.S. PATENT NO. 5,061,703

EXHIBIT LIST

A. Assignments of '703 Patent from Inventors to Merz

B. Consent of Patent Owner, Merz

C. Forest Power of Attorney

D. FDA Approval Letter for NAMENDA™ (memantine hydrochloride) (October 16, 2003)

E. U.S. Patent 5,061,703 ("the '703 patent")

F. Receipt for Payments of 3½, 7½, and 11½ Year Maintenance Fees for the '703 Patent

G. Cover Letter of Initial IND Submission (July 10, 1989)

H. Letter to FDA re: Inactivation of IND (January 13, 1994)

I. FDA Letter re: Receipt and Effective Date of Re-activated IND (December 23, 1997)

J. Chronology of Regulatory Review of NAMENDA™

K. Transfer of Ownership from Merz to Forest (September 13, 2000)

L. Cover Letter of NDA submitted to FDA (December 19, 2002)

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 3

Patent #: 5061703 **Issue Dt:** 10/29/1991 **Application #:** 07508109 **Filing Dt:** 04/11/1990

Inventors: JOACHIM BORMANN, MARKUS R. GOLD, WOLFGANG SCHATTON

Title: ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

Assignment: 1

Reel/Frame: 005302/0141 **Recorded:** 05/07/1990 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST.

Assignors: BORMANN, JOACHIM **Exec Dt:** 03/21/1990

GOLD, MARKUS R. **Exec Dt:** 03/21/1990

SCHATTON, WOLFGANG **Exec Dt:** 03/21/1990

Assignee: MERZ + CO. GBMH & CO., ECKENHEIMER LANDSTRASSE 100-104, D-6000 FRANKFURT AM MAIN 1, FEDERAL REPUBLIC OF GERMANY

Correspondent: GORDON W. HUESCHEN
715 THE "H" BUILDING
310 EAST MICHIGAN AVENUE
KALAMAZOO, MI 49007

Assignment: 2

Reel/Frame: 012865/0219 **Recorded:** 05/01/2002 **Pages:** 3

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: MERZ+CO. GMBH & CO. **Exec Dt:** 04/16/2002

Assignee: MERZ PHARMA GMBH & CO. KGAA, DBA MERZ PHARMACEUTICALS GMBH
ECKENHEIMER LANDSTRASSE 100
FRANKFURT-MAIN, GERMANY

Correspondent: THE FIRM OF HEUSCHEN AND SAGE
G. PATRICK SAGE
350 EAST MICHIGAN AVENUE
500 COLUMBIA PLAZA
KALAMAZOO, MI 49007

Assignment: 3

Reel/Frame: 013372/0354 **Recorded:** 10/09/2002 **Pages:** 3

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: MERZ PHARMA GMBH & CO. KGAA DOING BUSINESS AS MERZ PHARMACEUTICALS GMBH **Exec Dt:** 08/27/2002

Assignee: MERZ PHARMA GMBH & CO. KGAA
ECKENHEIMER LANDSTRASSE 100
FRANKFURT MAIN, GERMANY 60318

Correspondent: PATRICK SAGE
500 COLUMBIA PLAZA
350 EAST MICHIGAN AVENUE
KALAMAZOO, MI 49007

United States Patent [19]

Bormann et al.

[11] **Patent Number: 5,061,703**

[45] **Date of Patent: Oct. 29, 1991**

[54] **ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA**

[75] Inventors: **Joachim Bormann, Frankfurt; Markus R. Gold, Nauheim; Wolfgang Schatton, Eschborn, all of Fed. Rep. of Germany**

[73] Assignee: **Merz + Co. GmbH & Co., Frankfurt am Main, Fed. Rep. of Germany**

[21] Appl. No.: **508,109**

[22] Filed: **Apr. 11, 1990**

[30] **Foreign Application Priority Data**

Apr. 14, 1989 [EP] European Pat. Off. 89106657

[51] Int. Cl.[5] **A61K 31/13; A61K 31/41; A61K 31/55; A61K 31/445**

[52] U.S. Cl. **514/212; 514/325; 514/359; 514/662**

[58] Field of Search 514/212, 325, 359, 662

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

0227410 7/1987 European Pat. Off. .

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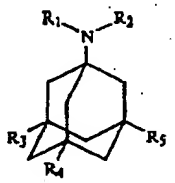
Hoyer, S.; Aging. 11, pp. 158–166 (1988).

Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

A method for the prevention and treatment of cerebral ischemia using an adamantane derivative of the formula



(I)

wherein

R_1 and R_2 are identical or different, representing hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof, is disclosed.

13 Claims, No Drawings

Merz 16

ASSIGNMENT

WHEREAS, We, (1) Joachim Bormann

(2) Markus R. Gold

(3) Wolfgang Schatton

(4) _____,

citizens of (1) Fed. Republic of Germany, (2) Fed. Republic of Germany

(3) Fed. Republic of Germany, and (4) _____ residing at

(1) Stalburgstrasse 36, D-6000 Frankfurt am Main 1

(2) Kranichstrasse 9, 6085 Nauheim

(3) Dornweg 11, 6236 Eschborn

(4) _____,

respectively, have invented certain new and useful improvements in

Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia

_____,

for which an application for United States Letters Patent was signed by us on even date herewith ; and

REEL 5302 FRAME 142

WHEREAS, Merz + Co. GmbH & Co.

having a place of business at Eckenheimer Landstrasse 100-104,

D-6000 Frankfurt am Main 1, FEDERAL REPUBLIC OF GERMANY

is desirous of acquiring the entire right, title, and interest in and to said invention and in and to any Letters Patent which may be granted therefor in the United States and in any and all foreign countries;

NOW, THEREFORE, in consideration of the sum of ONE DOLLAR ($1.00) to each of us in hand paid, the receipt whereof is hereby acknowledged, and other valuable consideration, we, the said (1) Joachim Bormann

(2) Markus R. Gold (3) Wolfgang Schatton and

(4) _____ have sold, assigned, and transferred, and by these presents do sell, assign, and transfer, unto said Merz + Co. GmbH & Co.

its successors and assigns, the full and exclusive right to the said invention in the United States and its territorial possessions and in

all foreign countries and the entire right, title, and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, and extensions thereof.

We hereby authorize and request the Patent Office Officials in the United States and in any and all foreign countries to issue any and all of said Letters Patent, when granted, to said

Merz + Co. GmbH & Co.,

as the assignee of the entire right, title, and interest in and to the same, for the sole use and behoof of said

Merz + Co. GmbH & Co.,

its successors and assigns.

RECORDED
PATENT AND TRADEMARK
OFFICE
MAY - 71990

FURTHER, We agree that we will communicate to said

Merz + Co. GmbH & Co.,

or its representatives, any facts known to us respecting said invention; testify in any legal proceeding; sign all lawful papers; execute all divisional, continuation, substitution, renewal, and reissue applications; execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to said

Merz + Co. GmbH & Co.,

its successors and assigns, make all rightful oaths; and generally do everything possible to aid said

Merz + Co. GmbH & Co.,

its successors and assigns, to obtain and enforce proper protection for said invention in the United States and in any and all foreign countries.

REEL 5302 FRAME 145

IN TESTIMONY WHEREOF, we have hereunto set our hands this ✓ 21 day of March ✓, 1990.

Signed in the presence of:

✓ Glaab
Witness (H. W. Glaab)

✓ Glaab
Witness (H. W. Glaab)

✓ Glaab
Witness (H. W. Glaab)

Witness

(1) Joachim Bormann

Signature: ✓ Joachim Bormann
Inventor

(2) Markus R. Gold

Signature: ✓ M. R. Gold
Inventor

(3) Wolfgang Schattor

Signature: ✓ W. Schattor
Inventor

(4)

Signature:
Inventor

Form PTO-240 (3-75)

U S DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

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DEPOSIT ACCOUNT ORDER FORM

BEFORE USING THIS ORDER FORM read the important information on the reverse side

MAIL TO: Commissioner of Patents and Trademarks, Washington, D.C. 20231

Date 5 3 90

Account No. 8 3220

Order No. 2428

Name and Address of Depositor:

GORDON W. HUESCHEN, ATTORNEY
715 The "B" Building
310 East Michigan Avenue
Kalamazoo, MI 49007

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ITEM OR SERVICE	VALUE FURNISHED ACTION OR U/M

DESCRIPTION OF ARTICLES OR SERVICES TO BE FURNISHED

PLEASE RECORD THE ATTACHED TWO-PAGE ASSIGNMENT

AGAINST SERIAL No. 07/508,109 filed April 11, 1990

AND RETURN TO THE UNDERSIGNED ATTORNEY.

RECEIVED
90 MAY 25 AM 7:28
ASSIGNMENT BRANCH

REEL 5302 FRAME 164

If additional space is needed attach separate sheet.

G.W. Hueschen
(Signature)

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PATENT AND TRADEMARK OFFICE
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RETURN AFTER FIVE DAYS

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715 The "B" Building
310 East Michigan Avenue
Kalamazoo, MI 49007

STREET ADDRESS

CITY, STATE, ZIP CODE

STOCK ORDER NO. 21085 05/24/90 07509109 08-3220 110 518 8.00CH

2428 Merz 16

TRADEMARK

OFFICE OF PUBLIC RECORDS

Docket No.: MERZ AG 116

FORM PTO-1595 (Modified)
(Rev. 03-01)
OMB No. 0651-0027 (exp.6/31/2002)
PGSAMREV03

RECORDATION FORM COVER SHEET
PATENTS ONLY

2002 MAY -1 AM 11

05-10-2002

102085101

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Tab settings → → → ▼ FINANCE SECTION ▼

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
MERZ + CO. GmbH & CO.

5.1.02

Additional name(s) of conveying party(ies) ☐ Yes ☒ No

2. Name and address of receiving party(ies):
MERZ PHARMA GmbH & CO. KGaA, dba
Name: MERZ PHARMACEUTICALS GmbH
Address: ECKENHEIMER LANDSTRASSE 100

City: FRANKFURT-MAIN State/Prov.:
Country: GERMANY ZIP: 60318

Additional name(s) & address(es) ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment ☐ Merger
☐ Security Agreement ☒ Change of Name
☐ Other

Execution Date: April 16, 2002

4. Application number(s) or patent numbers(s):

If this document is being filed together with a new application, the execution date of the application is:

Patent Application No.	Filing date
09/597,102	June 20, 2000
~~09/664,629~~	September 19, 2000
10/018,373	December 6, 2001

B. Patent No.(s)

5,061,703	6,034,134
5,288,501	6,071,966
5,382,601	
5,776,935	

Additional numbers ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: THE FIRM OF HUESCHEN AND SAGE
Registration No. 37710
Address: 500 COLUMBIA PLAZA
350 EAST MICHIGAN AVENUE

City: KALAMAZOO State/Prov.: MI
Country: USA ZIP: 49007

6. Total number of applications and patents involved: 9

7. Total fee (37 CFR 3.41):.....$ 360.00

☒ Enclosed - Any excess or insufficiency should be credited or debited to deposit account
☐ Authorized to be charged to deposit account

8. Deposit account number:
08-3220
(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

G. PATRICK SAGE — April 22, 2002

Name of Person Signing — Signature — Date

Total number of pages including cover sheet, attachments, and documents: 3

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

05/03/2002 TBIRZI 00000065 09597102
01 FC:581 360.00 OP

CHANGE OF COMPANY NAME

Merz + Co. GmbH & Co., a German company, does hereby state that it has changed its name to Merz Pharma GmbH & CO. KGaA, a German company, having a place of business at Eckenheimer Landstrasse 100, 60318 Frankfurt Main, Germany, which is doing business as Merz Pharmaceuticals GmbH, a fully owned subsidiary of Merz Pharma GmbH & CO. KGaA, having a place of business at Eckenheimer Landstrasse 100, 60318 Frankfurt Main, Germany. This Change of Company name is to be recorded against all of The United States and Worldwide Letters Patent and Patent Applications listed in Schedule A, attached hereto.

IN WITNESS WHEREOF, Merz + Co. GmbH & Co., a German company, has caused this instrument to be executed by its duly authorized representative as of this 16 day of APRIL, 2002.

MERZ + CO. GmbH & CO.

By: ppa. Pertschy
Name: DR. CHRISTIAN PERTSCHY
Title: EXECUTIVE DIRECTOR LEGAL DEPARTMENT

SCHEDULE A

UNITED STATES LETTERS PATENTS

Patent No.	Issue Date
5,061,703	29 OCT 1991
5,288,501	22 FEB 1994
5,382,601	17 JAN 1995
5,776,935	07 JUL 1998
6,034,134	07 MAR 2000
6,071,966	06 JUN 2000

UNITED STATES PATENT APPLICATIONS

Application No.	Filing Date
09/597,102	20 JUN 2000
09/664,629	19 SEP 2000
10/018,373	06 DEC 2001

Docket No.: MERZ AG 116

FORM PTO-1595 (Modified) (Rev. 03-01) OMB No. 0651-0027 (exp.5/31/2002) P06AREV03

RECOF 10-16-2002

U.S. DEPARTMENT OF COMMERCE Patent and Trademark Office

P

102250398

Tab settings ▶ ▶ ▶ ▼ ▼ ▼ ▼

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
MERZ PHARMA GMBH & CO. KGAA doing business as MERZ PHARMACEUTICALS GMBH

10-9-02

Additional name(s) of conveying party(ies) ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: MERZ PHARMA GMBH & CO. KGAA

Address: Eckenheimer Landstrasse 100

City: Frankfurt Main State/Prov.:

Country: Germany ZIP: 60318

Additional name(s) & address(es) ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment ☐ Merger

☐ Security Agreement ☒ Change of Name

☐ Other

Execution Date: 27 AUG 2002

4. Application number(s) or patent numbers(s):

If this document is being filed together with a new application, the execution date of the application is:

Patent Application No.	Filing date	B. Patent No.(s)
SEE SCHEDULE A		SEE SCHEDULE A

Additional numbers ☒ Yes ☐ No

2002 OCT -9 AM 8:50 OFFICE OF PUBLIC RECORDS FINANCE SECTION

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: G. PATRICK SAGE

Registration No. 37,710

Address: THE FIRM OF HUESCHEN AND SAGE

500 COLUMBIA PLAZA

350 EAST MICHIGAN AVENUE

City: KALAMAZOO State/Prov.: MI

Country: US ZIP: 49007

6. Total number of applications and patents involved: 9

7. Total fee (37 CFR 3.41):.....$ 360.00

☒ Enclosed - Any excess or insufficiency should be credited or debited to deposit account

☐ Authorized to be charged to deposit account

8. Deposit account number:

08-3220

(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

G. PATRICK SAGE — G. Patrick Sage — 9 October 2002

Name of Person Signing — Signature — Date

Total number of pages including cover sheet, attachments, and 3

Mail documents to be recorded with required cover sheet information to:
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Washington, D.C. 20231

10/15/2002 STBM11 00000120 5061703
01 FC:8021 350.00 OP

SCHEDULE A

UNITED STATES LETTERS PATENTS

Patent No.	Issue Date
5,061,703	29 OCT 1991
5,288,501	22 FEB 1994
5,382,601	17 JAN 1995
5,776,935	07 JUL 1998
6,034,134	07 MAR 2000
6,071,966	06 JUN 2000

UNITED STATES PATENT APPLICATIONS

Application No.	Filing Date
09/597,102	20 JUN 2000
09/664,629	19 SEP 2000
10/018,373	06 DEC 2001

CHANGE OF COMPANY NAME

MERZ PHARMA GMBH & CO. KGAA, doing business as Merz Pharmaceuticals GmbH, a German company, having a place of business at Eckenheimer Landstrasse 100, 60318 Frankfurt Main, Germany, does hereby state that it has changed its name to MERZ PHARMA GMBH & CO. KGAA, a German company, having a place of business at Eckenheimer Landstrasse 100, 60318 Frankfurt Main, Germany. This Change of Company name is to be recorded against all of The United States Letters Patent and Patent Applications listed in Schedule A, attached hereto.

IN WITNESS WHEREOF, MERZ PHARMA GMBH & CO. KGAA, a German company, has caused this instrument to be executed by its duly authorized representative as of this 27 day of August, 2002.

MERZ PHARMA GMBH & CO. KGAA

By: _____

Name: Dr. Christian Pertschy
Title: Attorney at Law
Executive Director Legal Department

EXPRESS MAIL CERTIFICATE

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I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to Mail Stop Patent Ext., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 by "Express Mail Post Office to Addressee" service.

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Name (Print) Signature

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Customer No.: 07278

Docket No.: 03269/8200177-000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,061,703

Inventors: Joachim BORMANN, Markus R. GOLD, and Wolfgang SCHATTON

Assignee: Merz Pharma GmbH & Co. KGaA

Title: ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

Issue Date: October 29, 1991

CONSENT OF PATENT OWNER

Mail Stop Patent Ext.
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Merz Pharma GmbH & Co. KGaA ("Merz"), a corporation having offices and doing business at Eckenheimer Landstrasse 100, 60318 Frankfurt am Main, Germany, is the assignee of the entire right, title, and interest in U.S. Patent No. 5,061,703 ("the '703 patent"), by virtue of assignments recorded at reel 005302, frame 0141 (recorded May 7, 1990); reel

012865, frame 0219 (recorded May 1, 2002); and reel 013372, frame 0354 (recorded October 9, 2002).

Merz hereby confirms that Forest Laboratories, Inc. ("Forest"), a corporation having offices and doing business at 909 Third Avenue, New York, N.Y. 10022, is the sole and exclusive licensee of the '703 patent by virtue of a license agreement between Merz and Forest. Merz hereby consents to and authorizes Forest to act on its behalf with regard to any application submitted to the U.S. Patent and Trademark Office for extension of the term of the '703 patent pursuant to 35 U.S.C. §156.

November 17, 2003

By: _____

Merz Pharma GmbH & Co. KGaA

Name: Dr. Christian Pertschy

Title: ~~Attorney at Law~~ Executive Director Legal Department

EXPRESS MAIL CERTIFICATE

Date _____ Label No. _____
I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to Mail Stop Patent Ext., Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 by "Express Mail Post Office to Addressee" service.

Name (Print) _____ Signature _____

PLEASE CHARGE ANY DEFICIENCY OR CREDIT ANY EXCESS IN THE FEES DUE WITH THIS DOCUMENT TO OUR DEPOSIT ACCOUNT NO. 04 - 0100

Customer No.: 07278

Docket No.: 03269/8200177-000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,061,703

Inventors: Joachim BORMANN, Markus GOLD, and Wolfgang SCHATTON

Assignee: Merz Pharma GmbH & Co. KGaA

Title: ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

Issue Date: October 29, 1991

POWER OF ATTORNEY

December 8, 2003

Mail Stop Patent Ext.
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Forest Laboratories, Inc. ("Forest"), acting as agent of the patent owner Merz Pharma GmbH & Co. KGaA ("Merz"), hereby appoints the attorneys and agents associated with customer no. 07278, all of the firm of DARBY & DARBY P.C., 805 Third Avenue, New York, NY 10022, to prosecute the accompanying Request for Extension of Patent Term and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please address all correspondence regarding this Request for Extension of Patent Term to:

Adda C. Gogoris, Esq.
Darby & Darby, P.C.
805 Third Avenue
New York, NY 10022
Tel: (212) 527-7700
Fax: (212) 753-6237

Forest Laboratories, Inc.

Date: 12/9/03

Name: [signature]

Title: VP - Finance & CFO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-487

Forest Laboratories, Inc.
Attention: Doreen V. Morgan, Pharm. D.
Harborside Financial Center
Plaza 3, Suite 602
Jersey City, NJ 07311

Dear Dr. Morgan:

Please refer to your new drug application (NDA) dated December 19, 2002, received December 19, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Namenda™ (memantine hydrochloride) 5 mg, 10 mg, 15 mg and 20 mg Tablets.

We acknowledge receipt of your submissions dated:

January 10, 2003	April 11, 2003	July 18, 2003	September 18, 2003
January 14, 2003	April 17, 2003	August 6, 2003	September 19, 2003
January 24, 2003	May 15, 2003	August 7, 2003	September 24, 2003
February 14, 2003	June 3, 2003	August 8, 2003	September 26, 2003
March 5, 2003	June 25, 2003	August 13, 2003	October 3, 2003
March 6, 2003	June 27, 2003	August 14, 2003	October 14, 2003
March 12, 2003	July 1, 2003	August 26, 2003	
March 13, 2003	July 3, 2003	August 29, 2003	
March 19, 2003	July 9, 2003	September 11, 2003	
March 24, 2003	July 11, 2003	September 12, 2003	

This new drug application provides for the use of Namenda™ (memantine hydrochloride) 5 mg, 10 mg, 15 mg and 20 mg Tablets for the treatment of moderate to severe dementia of the Alzheimer's type.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text and submitted labeling (immediate container and carton labels dated October 3, 2003, as amended dated October 14, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission "**FPL for approved NDA 21-487.**" Approval of this submission by FDA is not required before the labeling is used.

The approved expiration dating for Namenda™ tablets is 18 months at 25° C (77° F) and is based on the stability data provided in your December 19, 2002 submission. The expiration dating can be extended based on additional stability data generated and reported in the annual report.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you of your postmarketing study commitments in your submission dated October 14, 2003. These commitments are listed below.

1. The final study report for the ongoing renal impairment study (MEM-PK-02) should be submitted as a labeling supplement within 1 year of the date of approval.

2. A protocol for a study in subjects with moderate hepatic impairment compared to normal subjects should be submitted within 1 year from the date of approval and the final study report as a labeling supplement should be submitted within 18 months of FDA's acceptance of the protocol. This could be addressed by a post hoc analysis, if there are adequate number of hepatically impaired subjects in the clinical trials.

3. A protocol to evaluate the induction potential of memantine should be submitted within 6 months from the date of approval and the final study report should be submitted within 1 year from the date of approval.

4. Reanalyze the available ECG interval data (including data from study MEM-MD-06A) after all ECGs have been read by a central laboratory using standardized measuring methodology and submit the data within 6 months from the date of approval.

5. Submit additional eye examination results from the ongoing Allergan studies 192944-004-02 and 192944-005-02 and any other memantine studies where eye examination data are systematically collected by October 1, 2007.

Submit clinical protocols for the studies to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

We remind you that you must submit patent information on form FDA 3542, *Patent Information Submitted Upon and After Approval of an NDA or Supplement*, within 30 days of the date of this letter as required by 21 CFR 314.53(c)(2)(ii) and 314.53(d)(2) at the address provided by 21 CFR 314.53(d)(4). The form may be obtained at

http://www.fda.gov/opacom/morechoices/fdaforms/cder.html. To expedite review of this patent declaration form, we request you submit an additional copy of the form to this application and to the Center for Drug Evaluation and Research "Orange Book" staff at

Food and Drug Administration
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Melina Griffis, R.Ph., Senior Regulatory Project Manager at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

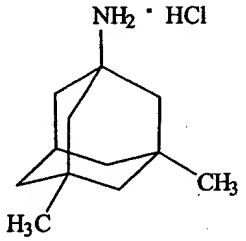
Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

R_x Only

DESCRIPTION

NAMENDA™ (memantine hydrochloride) is an orally active NMDA receptor antagonist. The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride with the following structural formula:



The molecular formula is $C_{12}H_{21}N \bullet HCl$ and the molecular weight is 215.76. Memantine HCl occurs as a fine white to off-white powder and is soluble in water. NAMENDA is available for oral administration as capsule-shaped, film-coated tablets containing 5 mg and 10 mg of memantine hydrochloride. The tablets also contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, talc and magnesium stearate. In addition the following inactive ingredients are also present as components of the film coat: hypromellose, triacetin, titanium dioxide, FD & C yellow #6 and FD & C blue #2 (5 mg tablets), iron oxide black (10 mg tablets).

CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacodynamics

Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's Disease.

Memantine showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca^{2+}, Na^{+} or K^{+} channels. Memantine also showed antagonistic effects at the $5HT_3$ receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency.

In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil, galantamine, or tacrine.

Pharmacokinetics
Memantine is well absorbed after oral administration and has linear pharmacokinetics over the therapeutic dose range. It is excreted predominantly in the urine, unchanged, and has a terminal elimination half-life of about 60-80 hours.

Absorption and Distribution
Following oral administration memantine is highly absorbed with peak concentrations reached in about 3-7 hours. Food has no effect on the absorption of memantine. The mean volume of distribution of memantine is 9-11 L/kg and the plasma protein binding is low (45%).

Metabolism and Elimination
Memantine undergoes little metabolism, with the majority (57-82%) of an administered dose excreted unchanged in urine; the remainder is converted primarily to three polar metabolites: the N-gludantan conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. These metabolites possess minimal NMDA receptor antagonist activity. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine. Memantine has a terminal elimination half-life of about 60-80 hours. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

Special Populations
Renal Impairment: Adequate information on the effect of renal impairment on the pharmacokinetics of memantine is not available. As the major route of elimination is renal, however, it is very likely that subjects with moderate and severe renal impairment will have significantly higher exposure than normal subjects.

Elderly: The pharmacokinetics of *NAMENDA™* in young and elderly subjects are similar.

Gender: Following multiple dose administration of *NAMENDA™* 20 mg b.i.d, females had about 45 % higher exposure than males,but there was no difference in exposure when body weight was taken into account..

Drug-Drug Interactions
Substrates of Microsomal Enzymes: In-vitro studies have shown that memantine produces minimal inhibition of CYP450 enzymes CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. These data indicate that no pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Inhibitors of Microsomal Enzymes: Since memantine undergoes minimal metabolism,with the majority of the dose excreted unchanged in urine, an interaction between memantine and drugs that are inhibitors of CYP 450 enzymes is unlikely.Co-administration of *NAMENDA™* with the AChE inhibitor donepezil HCl does not affect the pharmacokinetics of either compound.

Drugs Eliminated via Renal Mechanisms: Memantine is eliminated in part by tubular secretion. *In-vivo* studies have shown that multiple doses of the diuretic hydrochlorothiazide/triamterene (HCTZ/TA) did not affect the AUC of memantine at steady state. Memantine did not affect the bioavailability of TA, and decreased AUC and C_{max} of HCTZ by about 20%.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline state may lead to an accumulation of the drug with a possible increase in adverse effects. Drugs that alkalinize the urine (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) would be expected to reduce renal elimination of memantine.

Drugs highly bound to plasma proteins: Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely.

CLINICAL TRIALS

The effectiveness of NAMENDA (memantine hydrochloride) as a treatment for patients with moderate to severe Alzheimer's disease was demonstrated in 2 randomized, double-blind, placebo-controlled clinical studies (Studies 1 and 2) conducted in the United States that assessed both cognitive function and day to day function. The mean age of patients participating in these two trials was 76 with a range of 50-93 years. Approximately 66% of patients were female and 91% of patients were Caucasian.

A third study (Study 3), carried out in Latvia, enrolled patients with severe dementia, but did not assess cognitive function as a planned endpoint.
Study Outcome Measures: In each U.S. study, the effectiveness of NAMENDA was determined using both an instrument designed to evaluate overall function through caregiver-related assessment, and an instrument that measures cognition. Both studies showed that patients on NAMENDA experienced significant improvement on both measures compared to placebo.

Day-to-day function was assessed in both studies using the modified Alzheimer's Disease Cooperative Study – Activities of Daily Living inventory (ADCS-ADL). The ADCS-ADL consists of a comprehensive battery of ADL questions used to measure the functional capabilities of patients. Each ADL item is rated from the highest level of independent performance to complete loss. The investigator performs theinventory by interviewing a caregiver familiar with the behavior of the patient. A subset of 19 items, including ratings of the patients' ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores has been validated for the assessment of patients with moderate to severe dementia. This is the modified ADCS-ADL, which has a scoring range of 0 to 54, with the lower scores indicating greater functional impairment.

The ability of NAMENDA to improve cognitive performance was assessed in both studies with the Severe Impairment Battery (SIB), a multi-item instrument that has been

validated for the evaluation of cognitive function in patients with moderate to severe dementia. The SIB examines selected aspects of cognitive performance, including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment.

Study 1 (Twenty-Eight-Week Study)
In a study of 28 weeks duration, 252 patients with moderate to severe probable Alzheimer's disease (diagnosed by DSM-IV and NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥3 and ≤14 and Global Deterioration Scale Stages 5-6) were randomized to NAMENDA or placebo. For patients randomized to NAMENDA, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

Effects on the ADCS-ADL:
Figure 1 shows the time course for the change from baseline in the ADCS-ADL score for patients in the two treatment groups completing the 28 weeks of the study. At 28 weeks of treatment, the mean difference in the ADCS-ADL change scores for the NAMENDA - treated patients compared to the patients on placebo was 3.4 units. Using an analysis based on all patients and carrying their last study observation forward (LOCF analysis), NAMENDA treatment was statistically significantly superior to placebo.

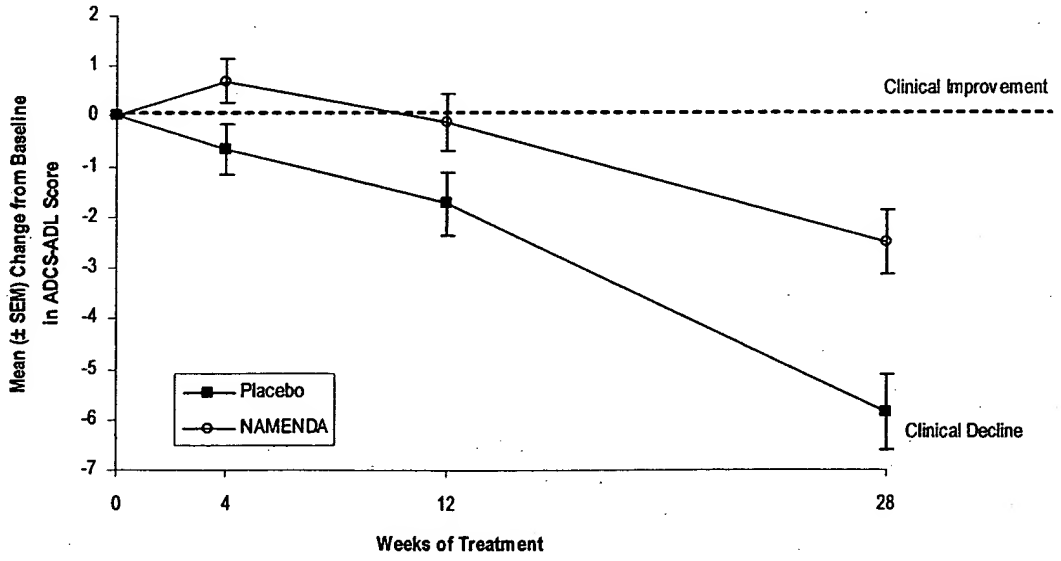


Figure 1: Time course of the change from baseline in ADCS-ADL score for patients completing 28 weeks of treatment.

Figure 2 shows the cumulative percentages of patients from each of the treatment groups who had attained at least the change in the ADCS-ADL shown on the X axis.
The curves shows that both patients assigned to NAMENDA and placebo have a wide range of responses and generally show deterioration (a negative change in ADCS-ADL compared to baseline), but that the NAMENDA group is more likely to show a smaller

decline or an improvement. (In a cumulative distribution display, a curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo.)

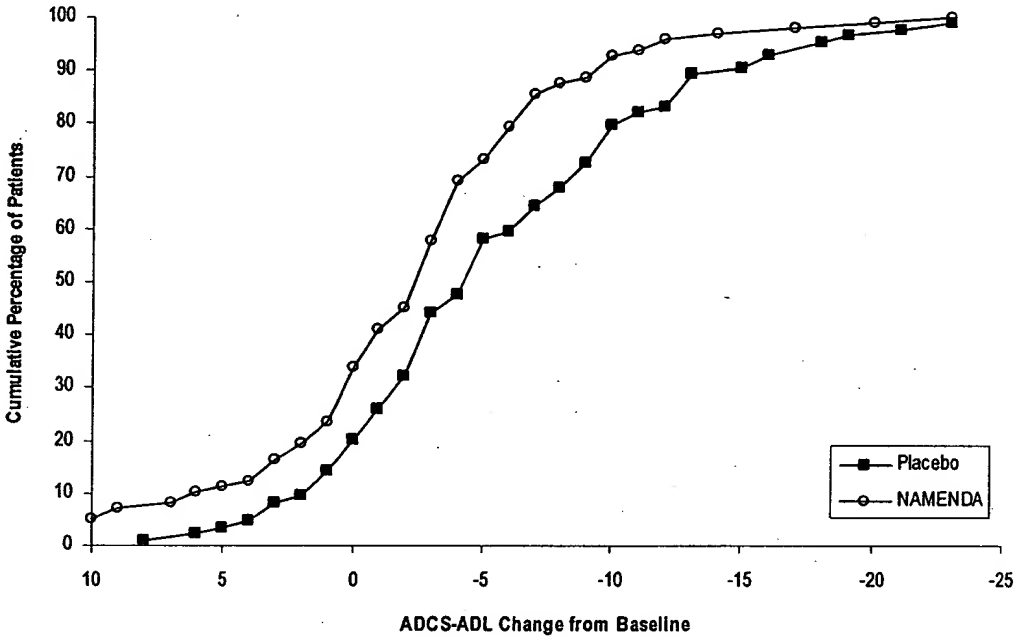


Figure 2: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB:

Figure 3 shows the time course for the change from baseline in SIB score for the two treatment groups over the 28 weeks of the study At 28 weeks of treatment, the mean difference in the SIB change scores for the NAMENDA™-treated patients compared to the patients on placebo was 5.7 units. Using an LOCF analysis, NAMENDA treatment was statistically significantly superior to placebo.

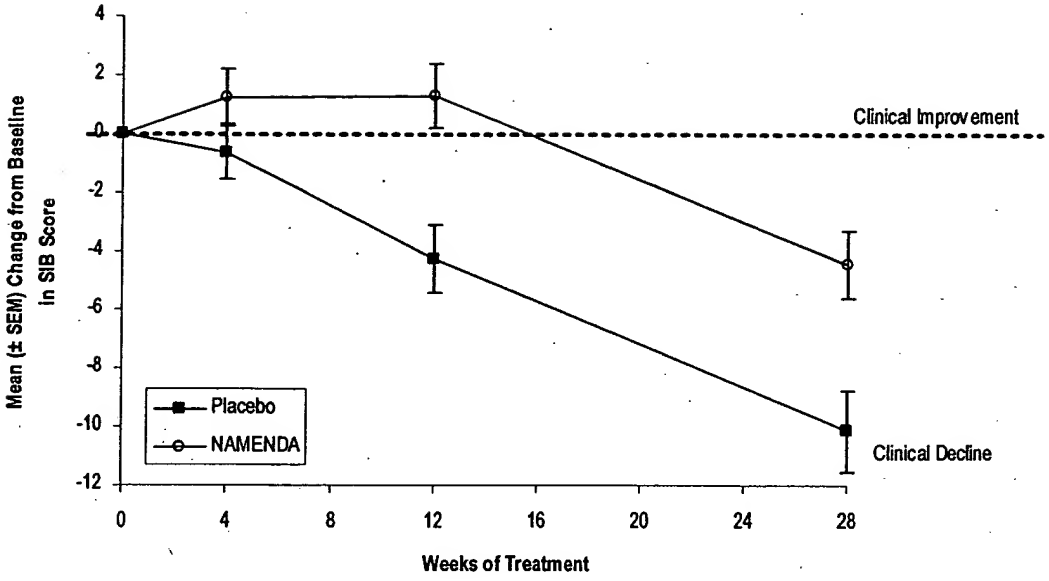


Figure 3: Time course of the change from baseline in SIB score for patients completing 28 weeks of treatment.

Figure 4 shows the cumulative percentages of patients from each treatment group who had attained at least the measure of change in SIB score shown on the X axis.

The curves show that both patients assigned to NAMENDA™ and placebo have a wide range of responses and generally show deterioration, but that the NAMENDA group is more likely to show a smaller decline or an improvement.

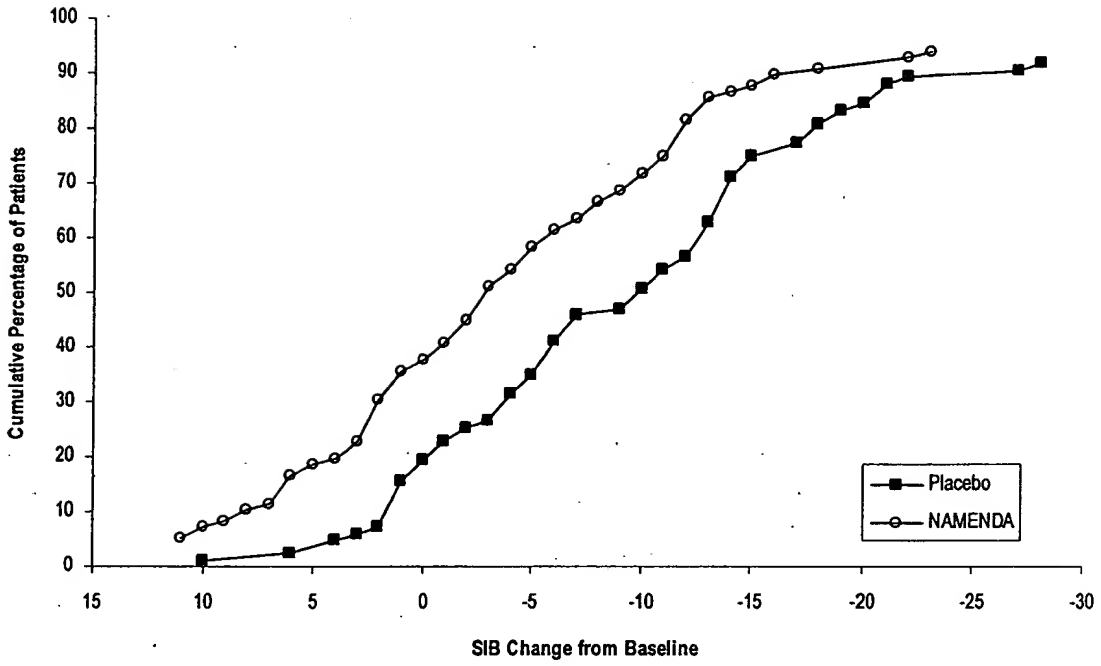


Figure 4: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Study 2 (Twenty-Four-Week Study)
In a study of 24 weeks duration, 404 patients with moderate to severe probable Alzheimer's disease (diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥5 and ≤14) who had been treated with donepezil for at least 6 months and who had been on a stable dose of donepezil for the last 3 months were randomized to NAMENDA™ or placebo while still receiving donepezil. For patients randomized to NAMENDA, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

Effects on the ADCS-ADL:
Figure 5 shows the time course for the change from baseline in the ADCS-ADL score for the two treatment groups over the 24 weeks of the study.At 24 weeks of treatment, the mean difference in the ADCS-ADL change scores for the NAMENDA/donepezil treated patients (combination therapy) compared to the patients on placebo/donepezil(monotherapy) was 1.6 units. Using an LOCF analysis, NAMENDA/donepezil treatment was statistically significantly superior to placebo/donepezil.

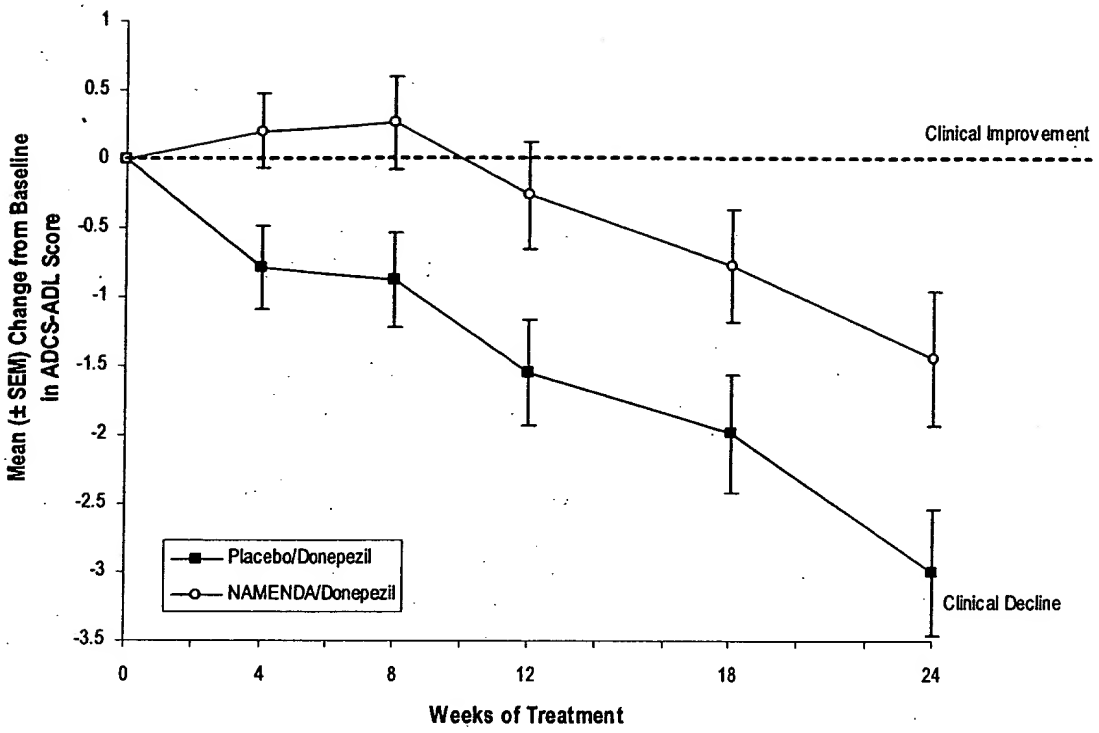


Figure 5: Time course of the change from baseline in ADCS-ADL score for patients completing 24 weeks of treatment.

Figure 6 shows the cumulative percentages of patients from each of the treatment groups who had attained at least the measure of improvement in the ADCS-ADL shown on the X axis.

The curves show that both patients assigned to NAMENDA/donepezil and placebo/donepezil have a wide range of responses and generally show deterioration, but that the NAMENDA/donepezil group is more likely to show a smaller decline or an improvement

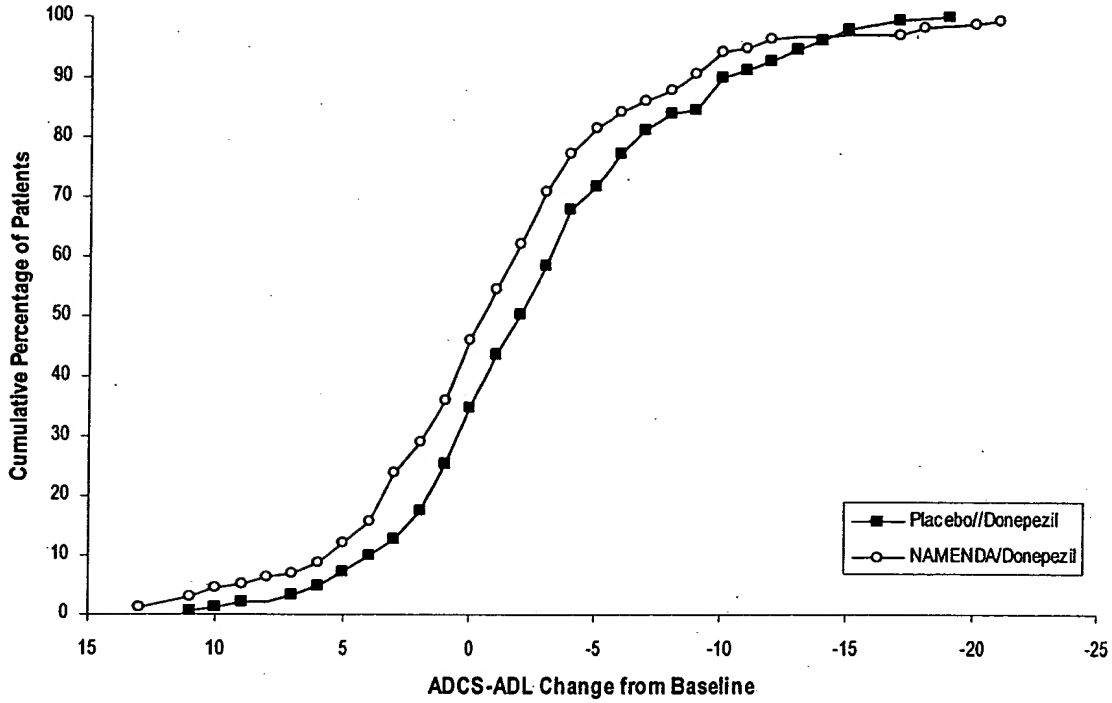


Figure 6: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB:

Figure 7 shows the time course for the change from baseline in SIB score for the two treatment groups over the 24 weeks of the study .At 24 weeks of treatment, the mean difference in the SIB change scores for the NAMENDA™/donepezil treated patients compared to the patients on placebo/donepezil was 3.3 units. Using an LOCF analysis, NAMENDA/donepezil treatment was statistically significantly superior to placebo/donepezil.

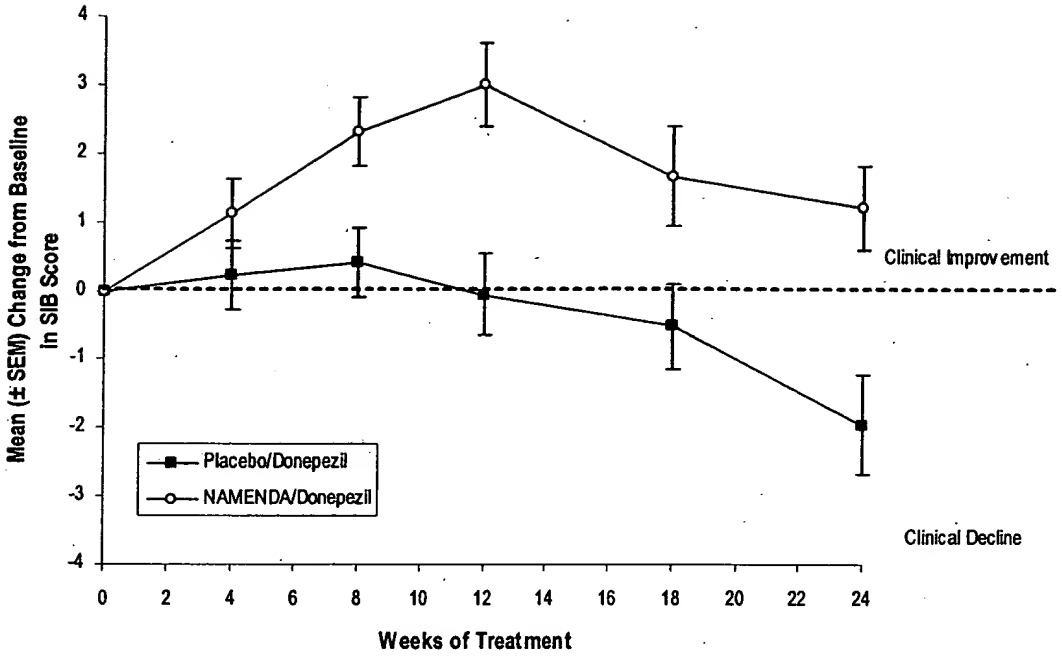


Figure 7: Time course of the change from baseline in SIB score for patients completing 24 weeks of treatment.

Figure 8 shows the cumulative percentages of patients from each treatment group who had attained at least the measure of improvement in SIB score shown on the X axis.

The curves show that both patients assigned to NAMENDA™/donepezil and placebo/donepezil have a wide range of responses, but that the NAMENDA/donepezil group is more likely to show an improvement or a smaller decline.

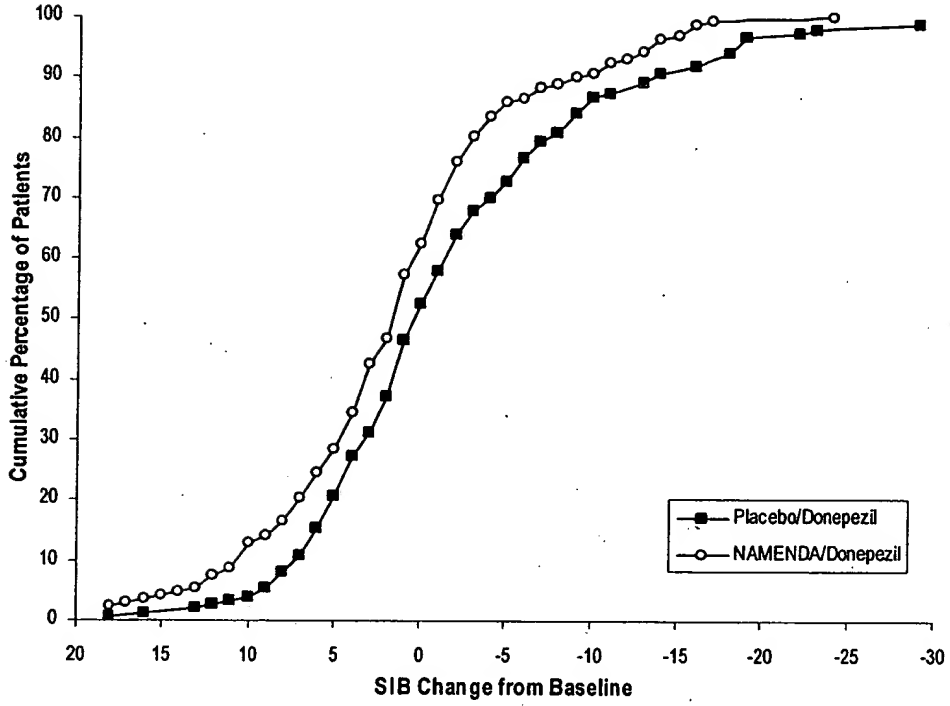


Figure 8: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Study 3 (Twelve-Week Study)

In a double-blind study of 12 weeks duration, conducted in nursing homes in Latvia, 166 patients with dementia according to DSM-III-R, a Mini-Mental Status Examination score of < 10, and Global Deterioration Scale staging of 5 to 7 were randomized to either NAMENDA™ or placebo. For patients randomized to NAMENDA, treatment was initiated at 5 mg once daily and increased to 10 mg once daily after 1 week. The primary efficacy measures were the care dependency subscale of the Behavioral Rating Scale for Geriatric Patients (BGP), a measure of day-to-day function, and a Clinical Global Impression of Change (CGI-C), a measure of overall clinical effect. No valid measure of cognitive function was used in this study. A statistically significant treatment difference at 12 weeks that favored NAMENDA over placebo was seen on both primary efficacy measures. Because the patients entered were a mixture of Alzheimer's Disease and Vascular dementia, an attempt was made to distinguish the two groups and all patients were later designated as having either vascular dementia or Alzheimer's Disease, based on their scores on the Hachinski Ischemic Scale at study entry. Only about 50% of the patients had computerized tomography of the brain. For the subset designated as having Alzheimer's Disease, a statistically significant treatment effect favoring NAMENDA over placebo at 12 weeks was seen on both the BGP and CGI-C.

INDICATIONS AND USAGE

NAMENDA™ (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS

NAMENDA ™ (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

PRECAUTIONS

Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

Neurological Conditions

Seizures: NAMENDA has not been systematically evaluated in patients with a seizure disorder. In clinical trials of NAMENDA, seizures occurred in 0.2% of patients treated with NAMENDA and 0.5% of patients treated with placebo.

Genitourinary Conditions

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

Special Populations

Hepatic Impairment

NAMENDA undergoes partial hepatic metabolism, but the major fraction of a dose (57-82%) is excreted unchanged in urine. The pharmacokinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected.

Renal Impairment

There are inadequate data available in patients with mild, moderate, and severe renal impairment but it is likely that patients with moderate renal impairment will have higher exposure than normal subjects. Dose reduction in these patients should be considered. The use of NAMENDA in patients with severe renal impairment is not recommended.

Drug-Drug Interactions

N-methyl-D-aspartate (NMDA) antagonists: The combined use of NAMENDA with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of NAMENDA *on substrates of microsomal enzymes:* In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4)

showed minimal inhibition of these enzymes by memantine. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of inhibitors and/or substrates of microsomal enzymes on NAMENDA*:* Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Co-administration of NAMENDA™ with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

Drugs eliminated via renal mechanisms: Because memantine is eliminated in part by tubular secretion, co-administration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of NAMENDA™ and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate,) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

Carcinogenesis, Mutagenesis and Impairment of Fertility

There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m^2 basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro S. typhimurium* or *E. coli* reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Pregnancy
Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the post-partum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m^2 basis.

There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether memantine is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

Pediatric Use
There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children.

ADVERSE REACTIONS

The experience described in this section derives from studies in patients with Alzheimer's Disease and Vascular Dementia.

Adverse Events Leading to Discontinuation: In placebo-controlled trials in which dementia patients received doses of NAMENDA™ up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the NAMENDA group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% or more of NAMENDA treated patients and at a rate greater than placebo.

Adverse Events Reported in Controlled Trials: The reported adverse events in NAMENDA (memantine hydrochloride) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ. Table 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with

NAMENDA™ than for those treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving NAMENDA and at a Higher Frequency than Placebo-treated Patients.

Body System Adverse Event	Placebo (N = 922) %	NAMENDA (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in NAMENDA-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, gait abnormal, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Vital Sign Changes: NAMENDA and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic

blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treatedwith NAMENDA. A comparison of supine and standing vital sign measures for NAMENDA and placebo in elderly normal subjects indicated that NAMENDA treatment is not associated with orthostatic changes.

Laboratory Changes: NAMENDA and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with NAMENDA™ treatment.

ECG Changes: NAMENDA and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with NAMENDA treatment.

Other Adverse Events Observed During Clinical Trials
NAMENDA has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Patients received NAMENDA treatment for periods of up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in Table 1, WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, e.g., because they are common in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to NAMENDA treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole: *Frequent:* syncope. *Infrequent:* hypothermia, allergic reaction.

Cardiovascular System: *Frequent:* cardiac failure. *Infrequent*: angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

Central and Peripheral Nervous System: *Frequent:* transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. *Infrequent:* paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemmorrhage, neuralgia, ptosis, neuropathy.

Gastrointestinal System: *Infrequent:* gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

Hemic and Lymphatic Disorders: *Frequent:* anemia. *Infrequent:* leukopenia.

Metabolic and Nutritional Disorders: *Frequent:* increased alkaline phosphatase, decreased weight. *Infrequent*: dehydration, hyponatremia, aggravated diabetes mellitus.

Psychiatric Disorders: *Frequent:* aggressive reaction. *Infrequent:* delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paroniria, delirium, depersonalization, neurosis, suicide attempt.

Respiratory System: *Frequent:* pneumonia. *Infrequent:* apnea, asthma, hemoptysis.

Skin and Appendages: *Frequent:* rash. *Infrequent:* skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria

Special Senses: *Frequent:* cataract, conjunctivitis. *Infrequent:* macula lutea degeneration, decreased visual acuity, decreased hearing, tinnitus, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment.

Urinary System: *Frequent:* frequent micturition. *Infrequent:* dysuria, hematuria, urinary retention

ADVERSE EVENTS FROM OTHER SOURCES

Memantine has been commercially available outside the United States since 1982, and has been evaluated in clinical trials including trials in patients with neuropathic pain, Parkinson's disease, organic brain syndrome, and spasticity. The following adverse events of possible importance for which there is inadequate data to determine the causal relationship have been reported to be temporally associated with memantine treatment in more than one patient and are not described elsewhere in labeling: acne, bone fracture, carpal tunnel syndrome, claudication, hyperlipidemia, impotence, otitis media, thrombocytopenia.

ANIMAL TOXICOLOGY

Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose on a mg/m^2 basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Memantine HCl is not a controlled substance.

Physical and Psychological Dependence: Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug.

As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine. In a documented case of an overdosage with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae.

DOSAGE AND ADMINISTRATION

The dosage of NAMENDA™ (memantine hydrochloride) shown to be effective in controlled clinical trials is 20 mg/day.

The recommended starting dose of NAMENDA is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week.

NAMENDA can be taken with or without food.

Doses in Special Populations
Dose reduction in patients with moderate renal impairment should be considered. In patients with severe renal impairment the use of NAMENDA™ has not been systematically evaluated and is not recommended. (See Clinical Pharmacology-Pharmacokinetics)

HOW SUPPLIED

5 mg Tablet:
Bottle of 60 NDC #0456-3205-60
Bottle of 200 NDC #0456-3205-21
Bottle of 2000 NDC #0456-3205-22
10 x 10 Unit Dose NDC #0456-3205-63
The capsule shaped film-coated tablets are tan, with the strength (5) debossed on one side and FL on the other.

10 mg Tablet:
Bottle of 60 NDC #0456-3210-60
Bottle of 200 NDC #0456-3210-21
Bottle of 2000 NDC #0456-3210-22
10 x 10 Unit Dose NDC #0456-3210-63
The capsule shaped film-coated tablets are gray, with the strength (10) debossed on one side and FL on the other.

Titration Pak:
PVC/Aluminum Blister package containing 49 tablets. 28 x 5 mg and 21 x 10 mg tablets.
NDC #0456-3200-14
The 5 mg capsule shaped film-coated tablets are tan, with the strength (5) debossed on one side and FL on the other. The 10 mg capsule shaped film-coated tablets are gray, with the strength (10) debossed on one side and FL on the other.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)[see USP Controlled Room Temperature]

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Robert Temple
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United States Patent [19]

Bormann et al.

[11] **Patent Number: 5,061,703**

[45] **Date of Patent: Oct. 29, 1991**

[54] **ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA**

[75] Inventors: **Joachim Bormann**, Frankfurt; **Markus R. Gold**, Nauheim; **Wolfgang Schatton**, Eschborn, all of Fed. Rep. of Germany

[73] Assignee: **Merz + Co. GmbH & Co.**, Frankfurt am Main, Fed. Rep. of Germany

[21] Appl. No.: **508,109**

[22] Filed: **Apr. 11, 1990**

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[5] **A61K 31/13**; A61K 31/41; A61K 31/55; A61K 31/445

[52] **U.S. Cl.** **514/212**; 514/325; 514/359; 514/662

[58] **Field of Search** 514/212, 325, 359, 662

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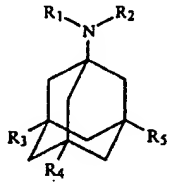
Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

A method for the prevention and treatment of cerebral ischemia using an adamantane derivative of the formula



(I)

wherein

R_1 and R_2 are identical or different, representing hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

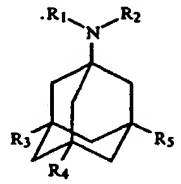
R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof, is disclosed.

13 Claims, No Drawings

ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

The present invention relates to a method for the prevention or treatment of cerebral ischemia using an adamantane derivative of the following general formula



(I)

wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic radical with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl; and

wherein

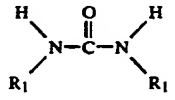
R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group, or a pharmaceutically-acceptable acid addition salt thereof. Herein branched or straight C_1–C_6 alkyl groups representatively include methyl, ethyl, iso- and n-propyl, n-, iso- and t-butyl, n-pentyl, n-hexyl, and the isomers thereof.

Certain 1-amino adamantanes of formula (I) are known. 1-amino-3,5-dimethyl adamantane, for example, is the subject matter of German patents 22 19 256 and 28 56 393.

Some 3,5-disubstituted 1-amino adamantanes of formula (I) are described in U.S. Pat. No. 4,122,193. 1-amino-3-ethyl adamantane is described in German Patent 22 32 735.

The compounds of formula (I) are generally prepared by alkylation of halogenated adamantanes, preferably bromo- or chloroadamantanes. The di- or tri-substituted adamantanes are obtained by additional halogenation and alkylation procedures. The amino group is introduced either by oxidation with chromiumtrioxide and bromination with HBr or bromination with bromine and reaction with formamide followed by hydrolysis. The amino function can be alkylated according to generally-accepted methods. Methylation can, for example, be effected by reaction with chloromethyl formate and subsequent reduction. The ethyl group can be introduced by reduction of the respective acetamide.

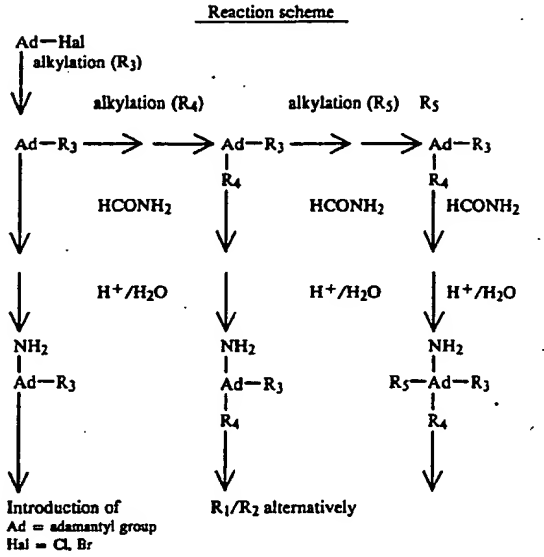
In accordance with U.S. Pat. No. 4,122,193 amination can also be effected by reaction of the respective 1-halogen-3,5- or -7-substituted adamantane with a urea derivative of the formula



wherein R_1 is hydrogen or alkyl.

The compounds according to formula (I) are prepared according to the following reaction scheme:

Reaction scheme



Alkylation of the halogenated adamantanes can be achieved by known methods, for example, through Friedel-Crafts reaction (introduction of phenyl group), or by reaction with vinylidene chloride, subsequent reduction and suitable Wittig reaction of the aldehydes and subsequent hydration, or by introduction of ethylene and subsequent alkylation with appropriate cuprates, or by introduction of ethylene and reduction of the halogen alkyl adamantanes, or by acylation with CO_2 and reduction of the carboxylic acid.

The compounds according to formula (I) known from the above-cited patents have so far been used for the treatment of parkinsonian and parkinsonoid diseases. Their mode of action is attributed to a dopaminergic influence on the CNS, either by an increased release of the transmitter substance dopamine or by an inhibition of its uptake. This compensates the imbalance of the dopamine/acetylcholine system.

In contrast to this type of disease, cerebral ischemia is characterized by a pathophysiological situation defined by an imbalance of neuronal stimulation mechanisms. In this context, the excessive inflow of calcium through NMDA receptor channels finally leads to the destruction of brain cells in specific brain areas (Rothmann & Olney, Trends Neurosci 10, 1989, pp. 299).

Therefore, in order to treat or eliminate this pathological situation, an antagonistic intervention is required with regard to the NMDA receptor channels (Kemp et al., Trends Pharmacol., Sci. 8, 1987. pp. 414).

Such intervention can, for example, be effected using substituted fluoro and hydroxy derivatives of dibenzo-[a,d]-cyclo-heptene-5,10-imine which are described in EP-A 0 264 183.

These heterocyclic, aromatic compounds are lipophilic and exhibit NMDA receptor channel-antagonistic and anticonvulsive properties. They are prepared by a relatively expensive method generating enantiomer mixtures which may be split into the individual optical antipodes.

The present invention is aimed at preparing and employing compounds which can be chemically generated

by simple methods, exhibiting an NMDA receptor channel-antagonistic and anticonvulsive action, for use in the prevention and treatment of cerebral ischemia.

This objective can be achieved according to the invention by using the 1-amino adamantanes of formula (I).

It has been found unexpectedly that the use of these compounds prevents an impairment or further impairment, i.e., degeneration and loss of nerve cells, after ischemia. Therefore, the adamantane derivatives of formula (I) are especially suited for the prevention and treatment of cerebral ischemia after apoplexy, open-heart surgery, cardiac standstill, subarachnoidal homorrhage, transient cerebro-ischemic attacks, perinatal asphyxia, anoxia, hypoglycemia, apnoea and Alzheimer's disease. The amount employed is a cerebral ischemia-alleviating or preventive amount.

Examples of compounds prepared and used according to the invention are:

1-amino adamantane
1-amino-3-phenyl adamantane
1-amino-methyl-adamantane
1-amino-3,5-dimethyl adamantane (test compound no. 1)
1-amino-3-ethyl adamantane (test compound no. 2)
1-amino-3-isopropyl adamantane (test compound no. 3)
1-amino-3-n-butyl adamantane
1-amino-3,5-diethyl adamantane (test compound no. 4)
1-amino-3,5-diisopropyl adamantane
1-amino-3,5-di-n-butyl adamantane
1-amino-3-methyl-5-ethyl adamantane
1-N-methylamino-3,5-dimethyl adamantane (test compound no. 5)
1-N-ethylamino-3,5-dimethyl adamantane (test compound no. 6)
1-N-isopropyl-amino-3,5-dimethyl adamantane
1-N,N-dimethyl-amino-3,5-dimethyl adamantane
1-N-methyl-N-isopropyl-amino-3-methyl-5-ethyl adamantane
1-amino-3-butyl-5-phenyl adamantane
1-amino-3-pentyl adamantane
1-amino-3,5-dipentyl adamantane
1-amino-3-pentyl-5-hexyl adamantane
1-amino-3-pentyl-5-cyclohexyl adamantane
1-amino-3-pentyl-5-phenyl adamantane
1-amino-3-hexyl adamantane
1-amino-3,5-dihexyl adamantane
1-amino-3-hexyl-5-cyclohexyl adamantane
1-amino-3-hexyl-5-phenyl adamantane
1-amino-3-cyclohexyl adamantane (test compound no. 7)
1-amino-3,5-dicyclohexyl adamantane
1-amino-3-cyclohexyl-5-phenyl adamantane
1-amino-3,5-diphenyl adamantane
1-amino-3,5,7-trimethyl adamantane
1-amino-3,5-dimethyl-7-ethyl adamantane (test compound no. 8)
1-amino-3,5-diethyl-7-methyl adamantane
1-N-pyrrolidino and 1-N-piperidine derivatives,
1-amino-3-methyl-5-propyl adamantane
1-amino-3-methyl-5-butyl adamantane
1-amino-3-methyl-5-pentyl adamantane
1-amino-3-methyl-5-hexyl adamantane
1-amino-3-methyl-5-cyclohexyl adamantane
1-amino-3-methyl-5-phenyl adamantane
1-amino-3-ethyl-5-propyl adamantane
1-amino-3-ethyl-5-butyl adamantane
1-amino-3-ethyl-5-pentyl adamantane
1-amino-3-ethyl-5-hexyl adamantane
1-amino-3-ethyl-5-cyclohexyl adamantane
1-amino-3-ethyl-5-phenyl adamantane
1-amino-3-propyl-5-butyl adamantane
1-amino-3-propyl-5-pentyl adamantane
1-amino-3-propyl-5-hexyl adamantane
1-amino-3-propyl-5-cyclohexyl adamantane
1-amino-3-propyl-5-phenyl adamantane
1-amino-3-butyl-5-pentyl adamantane
1-amino-3-butyl-5-hexyl adamantane
1-amino-3-butyl-5-cyclohexyl adamantane

their N-methyl, N,N-dimethyl, N-ethyl, N-propyl derivatives and their acid addition compounds.

Preferred compounds of formula (I) are those wherein R_1 and R_2 are hydrogen such as, for example, 1-amino-3-ethyl-5,7-dimethyl adamantane, and compounds wherein R_1, R_2, R_4 and R_5 are hydrogen such as, for example, 1-amino-3-cyclohexyl adamantane and 1-amino-3-ethyl adamantane.

Additional preferred compounds are those wherein R_1, R_2 and R_5 are hydrogen such as, for example, 1-amino-3-methyl-5-propyl or 5-butyl adamantane, 1-amino-3-methyl-5-hexyl or cyclohexyl adamantane, or 1-amino-3-methyl-5-phenyl adamantane.

Especially preferred compounds are 1-amino-3,5-dimethyl adamantane, 1-amino-3,5-diethyl adamantane, i.e., compounds wherein R_1, R_2 and R_5 are hydrogen, and compounds wherein R_1 and R_5 are hydrogen, R_2 is methyl or ethyl, and R_3 and R_4 are methyl such as, for example, 1-N-methylamino-3,5-dimethyl adamantane and 1-N-ethylamino-3,5-dimethyl adamantane.

The adamantane derivatives of formula (I) may be applied as such or in the form of their pharmaceutically-acceptable acid addition salts including, for example, the hydrochlorides, hydrobromides, sulfates, acetates, succinates or tartrates, or their acid addition salts with fumaric, maleic, citric, or phosphoric acids.

The compounds of formula (I) are administered in suitable form in doses ranging from about 0.01 to 100 mg/kg. Appropriate presentation forms are, for example, combinations of the active substance with common pharmaceutical carriers and adjuvants in the form of tablets, coated tablets, and sterile solutions or suspensions for injection. Pharmaceutically-acceptable carriers are, for example, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, gum arabic, corn starch, or cellulose, combined with diluents such as water, polyethylene glycol, etc. Solid presentation forms are prepared according to common methods and may contain up to 50 mg of the active ingredient per unit.

The efficacy of the compounds of formula (I) is described in the following pharmacological tests.

A. Displacement of TCP Binding

Phencyclidine (PCP), a known NMDA antagonist, binds to the NMDA receptor-associated ionic channel and blocks ionic transport (Garthwaite & Garthwaite, Neurosci. Lett. 83, 1987, 241–246). Additionally, PCP has been shown to prevent the destruction of brain cells after cerebral ischemia in rats (Sauer et al., Neurosci. Lett. 91, 1988, 327–332).

The interaction between compounds of formula (I) and the PCP bond is studied in the following. In this test ^{3}H-TCP, a PCP analogue, is used.

A membrane preparation of rat cortex is incubated with ^{3}H-TCP which is an analogue of phencyclidine (PCP) (Quirion & Pert 1982, Eur. J. Pharmacol. 83:155).

The interaction with the TCP binding is assessed for test compound no. 1 (1-amino-3,5-dimethyl adamantane) in a competitive experiment. This test shows that compound no. 1 is very effective in displacing TCP from the bond. The IC_{50} value is 89 nM. The conclusion can be drawn that compound no. 1 binds to NMDA receptor channels at the same site as the NMDA antagonist PCP.

B. Blocking of NMDA Receptor Channels

In the following test it is shown that the compounds of formula (I) according to the invention are as effective as PCP in blocking the NMDA receptor channel.

In the patch-clamp experiment, the current flowing through NMDA-activated membrane channels of cultivated spinal marrow neurons (mouse) is measured (Hamill et al 1981, Pflügers Arch. 312: 85–100). After application of 20 μM NMDA, the current signal of the cell is integrated for 20 sec. and recorded as a control answer (A_c). During succeeding application of 20 μM NMDA and 6 μM of an adamantane derivative, the intensity of the substance effect can be determined as a relative change of the control answer ($A/A_c - A$ = test answer).

The results are summarized in the following Table 1:

TABLE 1

Compound no.	1-A/Ac	n
1	0.66 ± 0.05	14
2	0.44 ± 0.08	7
3	0.58 ± 0.07	7
4	0.50 ± 0.11	5
5	0.56 ± 0.07	7
6	0.38 ± 0.05	7
7	0.25 ± 0.04	11
8	0.50 ± 0.03	6
PCP	0.50 ± 0.04	7
MK-801	0.60 ± 0.05	22

The values are given as means ± SEM.

As can be seen from the results, the aminoadamantane derivatives of formula (I) are able to block the NMDA receptor channel as has been described for PCP (Bertolini et al., Neurosci. Lett. 84, 1988, 351–355) and for 5-methyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5,10-imine (MK-801) (EP-A 0 264 183).

C. Anticonvulsive Effect

4, 12, 36, 108 and 324 mg/kg of the test substance is administered to mice by the intraperitoneal route (5 animals per dose). The supermaximum electroshock test is applied forty (40) minutes after application of the substance to investigate the anti-convulsive potential of the substance. The protected animals are added up over all dosages (score; maximum=25 animals).

The results are given in the following Table 2.

TABLE 2

Compound no.	Anticonvulsive action (score)	Mean	ED_{50} (mg/kg)
1	18		
	16		
	16		
	15	16.3	16
2	15		
	14		
	12	13.7	30
4	16		
	16		
	11	14.3	24
5	17		
	17	17.0	13
Standards:			
PCP	19	19.0	9
MK-801	25	25.0	<1

The ED_{50} values were estimated according to Litchfield, J. T. and Wilcoxon, F., J. Pharmacol. Exp. Therap. 96, 99–113 (1949).

As can be seen from the above results, aminoadamantane derivatives of formula (I) exhibit a protective effect against electrically induced convulsions. They therefore have an anticonvulsive effect.

D. Correlation Between Channel-Blocking and Anticonvulsive Action

The correlation between the action of the tested adamantane derivatives 1–8 at the NMDA receptor channel (in vitro) and the anticonvulsive effect (in vivo) has been tested. For this purpose an xy diagram of both test parameters is plotted. It shows that there is a correlation between the blocking of the NMDA receptor channel and the anticonvulsive action of the adamantanes of formula (I).

E. Protection Against Cerebral Ischemia

Both carotid arteries are occluded in rats for 10 minutes. At the same time the blood pressure is reduced to 60–80 mg Hg by withdrawal of blood (Smith et al. 1984, Acta Neurol. Scand. 69: 385, 401). The ischemia is terminated by opening the carotids and reinfusion of the withdrawn blood. After seven days the brains of the test animals are histologically examined for cellular changes in the CA1–CA4 region of the hippocampus, and the percentage of destroyed neurons is determined. The action of test compound No. 1 is determined after a single administration of 5 mg/kg and 20 mg/kg one (1) hour prior to the ischemia.

The results are summarized in the following Table 3:

TABLE 3

		Test compound no. 1	
Area	Control	5 mg/kg (n = 5)	20 mg/kg (n = 6)
CA1	80.2 ± 1.5	83.0 ± 2.2	53.1 ± 6.1**
CA3	3.6 ± 1.1	7.3 ± 1.8	2.7 ± 1.0
CA4	1.4 ± 0.4	3.7 ± 1.7	0.6 ± 0.3

The values are given in percent of damaged neurons ± SEM.
Significance of the mean difference: **p < 0.01 (U test)

The results show that the reduction of the post-ischemic neuronal brain damage in the CA1 region of the rat hippocampus is statistically significant after the pre-ischemic application of 20 mg/kg of test compound no. 1. Physiological parameters (e.g. blood pressure, body temperature) are not affected by the treatment. Moreover, the results show that the compounds according to formula (I) exhibit a neuroprotective action in cerebral ischemia.

Essentially the same result is attained by employing the compounds of the other Examples, especially those designated test compounds 2–8.

F. Protection Against NMDA-Induced Mortality

It is well known that, subsequent to cerebral ischemia, glutamate and aspartate levels increase massively in the brain. These excitatory aminoacids overstimulate

the NMDA-subtype of the glutamate receptor thus leading to delayed neuronal death. A similar pathophysiological situation is obtained when mice are administered intraperitoneally with 200 mg/kg NMDA. This high dose will eventually cause 100% mortality in the animals (Leander et al. 1984, Brain Res. 448; 115–120). We have found that the adamantane derivatives of the present invention are protective against the NMDA-induced mortality.

Compound No.	Dose mg/kg	Protected Animals
1	50	8/8
	25	6/8
	10	3/8
3	50	6/8
	25	4/8
4	50	7/8
	25	5/8
5	25	5/8

In the control animals, to which no adamantane was administered, the mortality was eight (8) animals out of eight (8).

G. Displacement of [^{3}H] MK-801 Binding in Human Brain Tissue

MK-801 binds to the ion channel associated with the NMDA receptor, as well as TCP does. This binding site is thought to mediate the neuroprotective effects of non-competitive NMDA-antagonists.

We have investigated whether the adamantane derivatives of the present invention are active at the MK-801 binding site. Tissue from frontal cortex was taken from patients at autopsy and homogenates were prepared. Inhibition of specific [^{3}H] MK-801 binding (3 nM) by the test compounds was determined (see e.g. Kornhuber et al. 1989, Eur. J. Pharmacol. 166: 589–590).

The test compounds were highly potent in displacing MK-801 binding, thus indicating a specific interaction with the NMDA receptor channel and predicting neuroprotective properties.

Compound No.	Ki nM
1	536
3	598
4	189
5	1607

wherein K_i is the inhibition constant and nM is nanomoles per liter. Mean values from triplicate experiments are given ± S.E.M.

The inhibition constant Ki is approximately equal to the concentration of the adamantane in nM required to displace 50% of the MK-801 specifically bound to the receptor. In this regard, memantine (Compound No. 1) was found to be the most potent compound subjected to this test, when compared with thirteen (13) other clinically-used and centrally-acting drugs, as reported in the foregoing publication.

The invention is further described by the following illustrative examples, which are not to be construed as limiting:

EXAMPLE 1

Injectable Solution

For preparing a 0.5% solution, dissolve 0.5% active ingredient and 0.8% sodium chloride (DAB 9) in doubly distilled water. Filter the solution through an antimicrobial filter, fill into 2-ml ampoules and sterilize for 20 minutes at 120° C. in an autoclave.

EXAMPLE 2

Solution

Dissolve 1% of active agent in demineralized water. Filter the solution before filling.

EXAMPLE 3

Tablets

1 tablet contains:	
Active ingredient	10.0 mg
Lactose	67.5 mg
Microcrystalline cellulose	18.0 mg
Talc	4.5 mg
	100.0 mg

The substances are mixed and the mixture compressed into 100-mg tablets in a direct tableting procedure without granulation.

EXAMPLE 4

Coated Tablets

Prepare 6-mm tablet cores of 100 mg as described under "Tablets". Coat the tablets in a sugar-coating process by coating the core with a sugar suspension first, followed by staining with a colored syrup and polishing.

The tablet coating consists of:

Sugar	65.0 mg
Talc	39.0 mg
Calcium carbonate	13.0 mg
Gum arabic	6.5 mg
Corn starch	3.7 mg
Shellac	1.1 mg
Polyethylene glycol 6000	0.2 mg
Magnesia usta	1.3 mg
Dye	0.2 mg
	130.0 mg

Total tablet weight: 230 mg

EXAMPLE 5

For preparing a 0.01% infusion solution, dissolve 0.01% of active ingredient and 5% levulose in doubly-distilled water. Filter the solution through an antimicrobial filter, fill into 500-ml infusion bottles, and sterilize.

The example provides 50 mg of active substance per single dose.

EXAMPLE 6

Synthesis of 1-Amino-3-isopropyl Adamantane Hydrochloride (Test Compound No. 3)

A. Preparation of Adamantane Methyl Carboxylate (I)

Stir 1.0 mol of adamantane carboxylic acid in 600 ml of methanol. Under ice cooling, drop 1.53 mol of acetyl chloride into the solution within 1 h. Remove the ice bath, and allow the reaction mixture to reach room temperature. Subsequently, heat for 3 hrs under reflux. Evaporate the reaction mixture to dryness under vacuum and distill. (Yield: 97%).

B. Preparation of Isopropyl Adamantane (II)

Introduce 0.5 mol of magnesium chips into 50 ml of absolute ether, and drop 0.5 mol of methyl iodide into the solution under moisture-free conditions until the ether boils. Subsequently, heat in a water bath until the magnesium has completely dissolved. Into this solution at room temperature drop 0.2 mol of adamantane methyl carboxylate in absolute ether. Then heat to reflux for 3 hours. After cooling, hydrolize with ice and mix with ammonium chloride solution until the precipitate has dissolved. Separate the ether phase, wash the aqueous phase with 2 portions of ether, and wash the combined organic phases with sodium bicarbonate solution. Then dry and evaporate to dryness under vacuum. (Yield: 93%).

C. Preparation of Isopropene Adamantane (III)

Stir 0.25 mol of isopropyl adamantane (II) in 500 ml acetic anhydride for 12 hours at 160° C. Subsequently, pour the reaction mixture onto 1 liter of ice water and extract with ether. Dry the combined organic phases with magnesium sulfate, filter, and evaporate to dryness under vacuum. Distill the residue under vacuum. (Yield: 66%).

D. Preparation of Isopropyl Adamantane (IV)

Dissolve 0.074 mol of adamantyl isopropene (III) in 100 ml of absolute ethanol. Add 4 g of palladium (5% on activated carbon) and hydrate under stirring for 24 hrs at room temperature. Subsequently, filter off the catalyst, and remove the solvent under vacuum. (Yield: 91%).

E. Preparation of 1-Bromo-3-isopropyl Adamantane (V)

Mix 0.034 mol of isopropyl adamantane (IV) with a ten times excess of bromine (0.33 mol). Heat slowly and stir under reflux for 4 h. Subsequently, allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until the aqueous solution has discolored. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

F. Preparation of 1-N-formyl-3-isopropyl Adamantane (VI)

Heat 0.028 mol of 1-bromo-3-isopropyl adamantane (V) with 40 ml of formamide to reflux for 12 hrs. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 82%).

G. Preparation of 1-Amino-3-isopropyl Adamantane Hydrochloride

Mix 0.023 mol of 1-N-formyl-3-isopropyl adamantane (VI) with 100 ml of 15% hydrochloric acid and heat to boiling for 24 hrs. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 57%).

EXAMPLE 7

Synthesis of 1-Amino-3-cyclohexyl Adamantane Hydrochloride (Test Compound No. 7)

A. Preparation of 1-Phenyl Adamantane (I)

Heat 0.068 mol of iron(III) chloride to boiling in 20 ml of absolute benzene. Drop 0.0186 mol of 1-bromo-adamantane, dissolved in 30 ml of absolute benzene, to the solution. Then heat to boiling for 3 hrs. After cooling, pour the reaction mixture onto ice/hydrochloric acid, separate the organic phase, and extract the aqueous phase with two portions of benzene. Wash the combined organic phases with water, dry with calcium chloride, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 80%).

B. Preparation of 1-Hydroxy-3-phenyl Adamantane (II)

To a solution of 0.03 mol chromiumtrioxide in 20 ml glacial acetic acid and 20 ml acetic anhydride, add 0.0095 mol of 1-phenyl adamantane at 0° C. and stir for 24 hours at 4° C. Pour the reaction mixture onto water and extract with three portions of pentane. Wash the organic phase with saturated sodium chloride solution, dry over magnesium sulfate, filter and evaporate to dryness under vacuum. Hydrolize the residue with 20 ml of 2N NaOH and 50 ml of methanol. Subsequently, remove the methanol under vacuum and dilute the residue with water. Then extract with three portions of ether. Dry the organic phase, filter and evaporate to dryness under vacuum. Recrystallize the residue from cyclohexane. (Yield: 50%).

Ref.: H. Stetter, M. Schwarz, A. Hirschhorn, Chem. Ber. (1959), 92, 1629–35.

C. Preparation of 1-Bromo-3-phenyl Adamantane (III)

Stir 0.03 mol of 3-phenyl adamantanol (II) with 100 ml of 40% HBr in glacial acetic acid for 20 min at 60° C. and 30 min at room temperature. Subsequently, dilute the reaction mixture with water and extract with ether. Wash the combined organic extracts with sodium chloride solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 68%).

Ref.: W. Fischer, C. A. Grog, Helvetica Chim. Acta (1976), 59, 1953.

D. Preparation of 1-N-formyl-3-phenyl Adamantane (IV)

Heat 0.03 mol of 1-bromo-3-phenyl adamantane (III) with 50 ml of formamide for 12 hrs to reflux. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 80%).

E. Preparation of 1-Amino-3-phenyl Adamantane Hydrochloride (V)

Heat 0.02 mol of 1-N-formyl-3-phenyl adamantane (IV) with 100 ml of 15% hydrochloric acid at reflux for 24 hours. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 60%).

F. Preparation of 1-Amino-3-cyclohexyl Adamantane (VI)

Dissolve 0.011 mol of 1-amino-3-phenyl adamantane (V) in 150 ml glacial acetic acid, mix with 0.3 g of platinum oxide (1% on activated carbon) and hydrate in a

Parr apparatus at 35° C. at a hydrogen pressure of 3 bar. Subsequently, remove the catalyst by filtration and evaporate the filtrate to dryness. Take up the residue in methanol and precipitate the product with ether. Suck off and dry. (Yield: 70%).

EXAMPLE 8

Synthesis of 1-Amino-3,5-dimethyl-7-ethyl Adamantane Hydrochloride (Test Compound No. 8)

A. Preparation of 1-Bromo-3,5-dimethyl Adamantane (I)

Mix 0.5 mol of 1,3-dimethyl adamantane with a ten times excess of bromine (5 mol). Slowly heat and stir for 4 hrs under reflux. Subsequently, allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discoloration of the aqueous solution. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

B. Preparation of 1-(2-Bromoethyl)-3,5-dimethyl Adamantane (II)

Mix 1.4 mol of 1-bromo-3,5-dimethyl adamantane (I) in hexane with 0.6 mol of aluminum bromide at −75° C. Subsequently, pass ethylene through the solution for 20–30 minutes, stir for 5 min., and pour the reaction mixture onto ice water. Extract with ether, dry the organic phase and evaporate to dryness. Recrystallize the residue from methanol. (Yield: 48%).

C. Preparation of 1,3-Dimethyl-5-ethyl Adamantane (III)

Dissolve 0.5 mol of 1-(2-bromoethyl)-3,5-dimethyl adamantane (II) in toluene, mix with 0.55 mol of sodium-bis(2-methoxy-ethoxy)dihydro aluminate, and heat to boiling for 3 hrs. After hydrolysis, separate the organic phase, dry with magnesium sulfate, and evaporate to dryness under vacuum. Purify the residue by vacuum distillation. (Yield: 86%).

D. Preparation of 1-Bromo-3,5-dimethyl-7-ethyl Adamantane (IV)

Mix 0.4 mol of 1,3-dimethyl-5-ethyl adamantane (III) with a ten times excess of bromine (4 mol). Heat slowly and stir for 4 hrs under reflux. Subsequently allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discolouration of the aqueous solution. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 86%).

E. Preparation of 1-N-formyl-3,5-dimethyl-7-ethyl Adamantane (V)

Heat 0.2 mol of 1-bromine-3,5-dimethyl-7-ethyl adamantane (IV) with 150 ml of formamide at reflux for 12 hrs. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 82%).

F. Preparation of 1-Amino-3,5-dimethyl-7-ethyl Adamantane Hydrochloride (VI)

Mix 0.2 mol of 1-N-formyl-3,5-dimethyl-7-ethyl adamantane (V) with 100 ml of 15% hydrochloric acid and heat to boiling for 24 hrs. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 57%).

EXAMPLE 9

Synthesis of 1-N-methylamino-3,5-dimethyl Adamantane (Test Compound No. 5)

Dissolve 0.1 mol of the appropriately substituted amino adamantane (1-amino-3,5-dimethyl adamantane) with 0.15 mol of chloromethyl formate and potassium carbonate in acetone and heat to reflux for 8 hrs. After cooling, filter the solution, remove the solvent and dry the residue. Mix the raw product (0.05 mol) with 0.1 mol of sodium-bis-(2-methoxy-ethoxy)-dihydro aluminate in toluene and heat at reflux for 3 hrs. After cooling, hydrolize with dilute HCl, dry the organic phase and evaporate to dryness. Purify the raw material by distillation.

EXAMPLE 10

Synthesis of 1-Amino-3-ethyl-5-phenyl Adamantane

A. Preparation of 1-Bromo-3-ethyl Adamantane (I)

Mix 0.034 mol of ethyl adamantane with a ten times excess of bromine (0.33 mol). Heat slowly and stir under reflux for 4 hrs. Then allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discoloration of the aqueous solution. Subsequently extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

B. Preparation of 1-Ethyl-3-phenyl Adamantane (II)

Heat 0.068 mol of iron(III) chloride in 20 ml of absolute benzene to boiling. Drop 0.0186 mol of 1-bromo-3-ethyl adamantane (I), dissolved in 30 ml of absolute benzene, into the solution. Then heat at reflux for 3 hrs. After cooling, pour the reaction mixture onto ice/hydrochloric acid, separate the organic phase, and extract with two portions of benzene. Wash the combined organic phases with water, dry with calcium chloride, filter and evaporate to dryness. Recrystallize the residue from methanol. (Yield: 80%).

C. Preparation of 1-Ethyl-3-hydroxy-5-phenyl Adamantane (III)

To a solution of 0.03 mol of chromiumtrioxide, in 20 ml glacial acetic acid and 20 ml acetic anhydride, add 0.0095 mol of 1-ethyl-3-phenyl adamantane (II) at 0° C. and stir for 24 hours at 4° C. Pour the reaction mixture into water and extract with three portions of pentane. Wash the organic phase with saturated sodium chloride solution, dry over magnesium sulfate, filter and evaporate to dryness under vacuum. Hydrolize the residue with 20 ml of 2N NaOH and 50 ml of methanol. Remove the methanol under vacuum and dilute the residue with water. Then extract with three portions of ether. Dry the organic phase, filter and evaporate to dryness under vacuum. Recrystallize the residue from cyclohexane. (Yield: 50%).

Ref.: H. Stetter, M. Schwarz, A. Hirschhorn, Chem. Ber. (1959), 92, 1629–35.

D. Preparation of 1-Bromo-3-ethyl-5-phenyl Adamantane (IV)

Stir 0.03 mol of 1-ethyl-3-hydroxy-5-phenyl adamantane (III) with 100 ml of 40% HBr in glacial acetic acid for 20 min at 60° C. and for 30 min at room temperature. Subsequently dilute the reaction mixture with water and extract with ether. Wash the combined organic extracts with sodium chloride solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 68%).

Ref.: W. Fischer, C. A. Grog, Helvetica Chim. Acta (1976), 59, 1953.

E. Preparation of 1-N-formyl-3-ethyl-5-phenyl Adamantane (V)

Heat 0.03 mol of 1-ethyl-3-hydroxy-5-phenyl adamantane (IV) with 50 ml of formamide for 12 hrs at reflux. After cooling, pour the reaction mixture into water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness. (Yield: 80%).

F. Preparation of 1-Amino-3-ethyl-5-phenyl Adamantane Hydrochloride (VI)

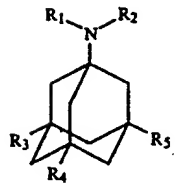
Heat 0.02 mol of 1-N-formyl-3-ethyl-5-phenyl adamantane (V) with 100 ml of 15% hydrochloric acid for 24 hrs at reflux. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 60%).

It is thus seen that certain adamantane derivatives, some of which are novel, have been provided for the prevention and treatment of cerebral ischemia, and that pharmaceutical compositions embodying such an adamantane derivative have been provided for use in the prevention and treatment of cerebral ischemia, the amount of the said adamantane derivative provided in either case being a cerebral ischemia-alleviating or preventive amount.

Various modifications and equivalents will be apparent to one skilled in the art and may be made in the compounds, compositions, methods, and procedures of the present invention without departing from the spirit or scope thereof, and it is therefore to be understood that the invention is to be limited only by the full scope which can be legally attributed to the appended claims.

We claim:

1. A method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof, an effective amount of an adamantane derivative of the general formula



(I)

wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof.

2. A method according to claim 1, wherein R_1, R_2 and R_5 are hydrogen.

3. A method according to claim 2, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are methyl.

4. A method according to claim 2, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are ethyl.

5. A method according to claim 1, wherein R_1, R_2, R_4 and R_5 are hydrogen, and R_3 is ethyl, isopropyl, or cyclohexyl.

6. A method according to claim 1, wherein R_2 and R_5 are hydrogen.

7. A method according to claim 6, wherein R_3 and R_4 are methyl, R_2 and R_5 are hydrogen and R_1 is methyl or ethyl.

8. A method according to claim 1, wherein R_1 and R_2 are hydrogen.

9. A method according to claim 8, wherein R_1 and R_2 are hydrogen, R_3 is ethyl, and R_5 and R_4 are methyl.

10. A method according to claim 1 for the treatment of Alzheimer's disease.

11. A method of claim 1, wherein the adamantane derivative is administered in an effective cerebral ischemia-alleviating or preventive amount.

12. A method of claim 11, wherein the adamantane derivative is administered in the form of a composition containing the same together with a pharmaceutically-acceptable carrier or diluent.

13. A method of claim 11, wherein the adamantane derivative is administered in an amount effective to prevent degeneration and loss of nerve cells after ischemia.

* * * * *

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Maintenance Fee Statement

5061703

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYME ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURIN THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,061,703	183	960	0	07/508,109	10/29/91	04/11/90	04	NO	PAID

25666

ITEM NBR	ATTY DKT NUMBER
1	MERZ16

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ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,061,703	184	1900	0	07/508,109	10/29/91	04/11/90	08	NO	PAID

25666

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ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,061,703	1553	3150	0	07/508,109	10/29/91	04/11/90	12	NO	PAID

25666

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1	MERZ16

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2057 Summit Dr.
Lake Oswego
Oregon 97034
USA

Telephone: (503) 636-3281
FAX: (503) 636-6902
TELEX: 6502308500
Residence: (503) 636-4427

July 10, 1989

Paul D. Leber, M.D.
Division of Neuropharmacological
Drug Products (HFD-120)
Food and Drug Administration
5600 Fishers Lane
Room 10B45
Rockville
Maryland 20857

Re: **Initial IND Submission--Memantine®**

Dear Dr. Leber:

Enclosed please find an original and two (2) copies of an Investigational New Drug Application ("IND") for Memantine® sponsored by Merz + Co. GmbH & Co., Eckenheimer Landstraße 100, D-6000 Frankfurt/Main 1, Federal Republic of Germany.

Our firm, BIO-SYSTEMS RESEARCH, is the sponsor's authorized representative in the United States for Merz. If you have any questions regarding the IND please do not hesitate to call me.

Regards,

Arthur J. Saffir, D.M.D., Ph.D.
President

G.H. Besselaar Associates
Princeton Research Center
103 College Road East
PRINCETON, NJ 08540-6681
USA
Phone (609) 452 8550
Fax (609) 452 9375

13 January 1994
Serial No. 012

Paul Leber, M.D.
Division Director
Food and Drug Administration
Division of Neuropharmacological
Drug Products (HFD-120)
Document Control Room 10B-20
5600 Fishers Lane
Rockville, Maryland 20857

BESSELAAR

Re: IND 33,392/Memantine
Other: Inactivation of IND

Dear Dr. Leber:

Acting as agent for Merz + Co. GmbH & Co. for the above noted IND for memantine, we wish to inactivate this IND 33,392.

The last Annual Report for memantine under this IND was submitted on 13 September 1993 as Serial No. 011. As indicated in that report no clinical studies were undertaken in the annual reporting period. No clinical studies have occurred since that submission and no clinical studies are planned in the near future. We are cognizant of the provisions and responsibilities for an IND on inactive status as presented in 21 CFR 312.45. All of the submissions and correspondence that relate to IND 33,392 will remain on file at G. H. Besselaar Associates.

If you have any questions regarding this submission, we would be pleased to respond.

Sincerely,

Hockel

Gregory M. Hockel, Ph.D.
Senior Director, Regulatory Affairs

RJW/GMH;egd
ref.ltrs/inactive.ind

bcc: J. P. Burns, Jr., Ph.D.
N. S. Kirchof
P. F. Kosmoski
T. J. Newman, M.D.
R. J. Wojnar, Ph.D.
Dr. R. Rischke (Merz & Co.)

IND 33,392

Food and Drug Administration
Rockville MD 20857

Covance Clinical and Periapproval Services Inc. U.S. Agent for: Merz + Co.
Attention: Catherine Michel, Ph. D.
210 Carnegie Center
Princeton, NJ 08540

DEC 23 1997

Dear Dr. Michel:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(I) of the Federal Food, Drug, and Cosmetic Act for Memantine.

We also refer to a telephone conversation between you and Ms. Katurah Higgins of this Division on October 9,1997.

We have completed our review of your submission dated September 5,1997, and as communicated to you by Ms. Katurah Higgins on October 9,1997, we have no objection to the initiation of your proposed clinical study. However, we have the following additional comments and requests:

Clinical

For the indication of a symptomatic treatment for Alzheimer's disease, efficacy studies should demonstrate clinically significant changes on a cognitive scale as well as a clinical global assessment. We recommend that you designate a valid assessment of cognitive function as one of the primary outcome measures.

Investigator's Brochure

In general, we note several statements that are promotional regarding efficacy and dismissive regarding potential toxicities. We remind you that the Investigator's Brochure should not contain any statements that imply any established efficacy, and should clearly state the potential toxicities so that they can be monitored for in the clinical trials. Some examples are as follows; please note that this list is not exhaustive and that we request you to review the entire Investigator's Brochure for other statements which need to be modified or omitted. (We also refer you to the Divisions letters of November 20, 1992 and March 3, 1993, which noted many problems with the originally submitted Investigator's Brochure, some of which are still present in the current Investigator's Brochure):

1. Page 6 - The list of "Therapeutic indications" should be omitted.

2. Page 9 - The following are misleading and/or promotional:
"...indicative for its utility as therapy of choice for the treatment of cerebral deficits..."; "These actions ... are the basis for the clinical observations that..."; "NMDA antagonists might be of therapeutic value in diverse conditions such

as..."; "the list of mechanism-based assumptions on probable indications is still growing..."; "Memantine's action on dementia syndrome can be ascribed to...".

3. Page 27, 6th and 7th paragraphs - A mg/kg comparison between animals and humans (with the implication that the animal findings are irrelevant to humans) is misleading.

4. Page 29- The phrase "which is not harmful" should be omitted.

5. Page 30- The use of "safety factors" is misleading.

6. Page 31 - The second paragraph, implying that the human risk is known because the drug was tested in animals at "many times the human therapeutic dose" is speculative and misleading.

   The statement that the "Olney lesion" was not seen in baboons should note that no positive control was used.

   The last 2 paragraphs, as well as the first paragraph on page 32, implying that the "Olney lesion" will not occur in humans, should be omitted.

7. Page 32 - The statement the "Olney lesions" "appear to be a rodent-specific toxic reaction to high bolus doses.. .which cannot be extrapolated to .. humans" should be omitted.

8. The section on the animal toxicity studies (p. 27-30) should include a more detailed summary of the methods used and salient results obtained in each study.

Biopharmaceutics

1. We note that the Investigator's Brochure (P.43 of 78) concludes that memantine human pharmacokinetic findings support twice-daily oral dosing. Since memantine has a long half-life of approximately 70 - 90 hours, please provide a rationale for twice-daily dosing.

2. Since memantine is primarily eliminated unchanged via renal excretion, the exclusion criteria should provide for the exclusion of concomitant administration of medications with the potential for interfering with renal excretion, eg., probenecid.

3. You are encouraged to characterize the pharmacokinetics of memantine in the subset of patients participating in the clinical trial.

4. Please consider collecting sparse plasma samples in the proposed clinical trial and explore the PK/PD efficacy and adverse events of the drug.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and its implementing regulations promulgated there under. This includes reporting any unexpected fatal or life threatening experiences with the drug to FDA by telephone within three working days after receipt of the information (21 CFR 312.32), and the submission of annual progress reports at intervals not to exceed one year.

Your future submissions should be in triplicate and addressed as follows:

Division Director
Food and Drug Administration
Division of Neuropharmacological Drug Products (HFD-120)
5600 Fishers Lane
Rockville, Maryland 20857

Each submission should be accompanied by a cover letter which identifies your IND number and explicitly enumerates the contents of your submission.

If you have any questions concerning this IND, please contact Ms. Melina Malandrucco, Regulatory Management Officer, at (301) 594-5526.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-00		Dementia	/000: Initial IND Submission (for spasticity of various origin) Protocol: efficacy of memantine compared to placebo in the treatment of spasticity in multiple sclerosis (On Sept. 19, 1989 received FDA letter placing on clinical hold)	7/10/89	Merz
	25-78-02			/003: Annual Report (As per annual report, no US studies have begun yet)	4/29/91	Merz
	25-78-03		Memantine HCl (Merz/Quintiles) Dementia	/004: Identifies G.H. Besselaar Associates as the New U.S. Agent	1/23/92	Merz

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-04			/005: Protocol Amendment: New Protocol # GHBA-186 for new indication, Dementia. Title "a double-blind dose-finding safety and efficacy study of memantine Akatinol in Alzheimer's disease"	7/31/92	Merz
	25-78-11			/006: Response to FDA Request for Information via Phone on 8/6/92 with Regard to New Protocol GHBA-186 (Acknowledges that IND therapeutic indication would change to Alzheimer's dementia and IND number would remain the same)	8/13/92	Merz

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-13			/008: Response to Clinical Hold-Revised Investigator's Brochure Dated 1/93 (IND was place on clinical hold via phone on 3/4-Sept.-1992. FDA wanted promotional statements from IB removed and a more complete discussion of animal tox. studies; followed up with FDA letter on 20-Nov-1992)	1/20/93	Merz
	25-78-18		Memantine HCl (Merz/Quintiles) Dementia	/011: IND Annual Report (As of Sept. 13, 1993, no studies were conducted during past year)	9/13/93	Merz
	25-78-22			/012: Other: Request for Inactivation of IND	9/13/94	Merz

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-23			/013: Reactivation of IND - Submission of Clinical Protocol MRZ-90001-9605, Dated 8/15/97 37 volumes	8/29/97	Merz
	25-78-61			/014: IND Safety Report	11/21/97	Merz
	25-78-61A			/014A: Request for "End-of-Phase II" - Meeting	12/17/97	Merz
	25-78-62		Memantine HCl (Merz/Quintiles) Dementia	/015: Request for "End-of-Phase II" - Meeting	2/06/98	Merz
	25-78-63			/016: IND Transfer	2/18/98	Merz
	25-78-64			/017: Other: End of Phase II Meeting - Briefing Documents	2/14/98	Merz
	25-78-65			/018: Other: Minutes of CMC Teleconference	3/17/98	Merz
	25-78-66			/019: IND Safety Report	3/22/98	Merz

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-67			/021: IND Safety Report	3/27/98	Merz
	25-78-68			/022: Other: Revised Minutes of Clinical Meeting of 2/18/98	4/08/98	Merz
	25-78-69			/023: Other: Response to FDA Comments on Sponsor End-of-Phase II Meeting Minutes	5/22/98	Merz
	25-78-70		Memantine HCl (Merz/Quintiles) Dementia	/024: Other: Notification of Cross-Reference Authorization	6/10/98	Merz
	25-78-71			/025: Other: Request for a Deviation to the Safety Reporting Requirements in 21 CFR 312.32	8/13/98	Merz

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-72			/026: Other: Request for Response to Outstanding Nonclini-cal Discussion Point from the End-to-Phase II Meeting	8/18/98	Merz
	25-78-73			/027: IND Safety Report	9/14/98	Merz
	25-78-74			/028: Protocol Amendment: New Proto- col New Investi-gators; for Protocol #90001-9605 Provided in Amendment #23, (5/22/98) for Comment Volume 1 of 3	9/18/98	Merz
	25-78-75		Memantine HCl (Merz/Quintiles) Dementia	Volume 2 of 3	9/18/98	Merz
	25-78-76			Volume 3 of 3	9/18/98	Merz

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-77			/029: Information: Notification of a New Manufacturer for the Active Ingredient and Update to Packaging Specifications	10/12/98	Merz
	25-78-78			/030: Protocol Amendment: New Investigator	10/16/98	Merz
	25-78-79			/031: Annual Report 10/9/97 - 10/9/98 Volume 1 of 25	12/07/98	Merz
	25-78-80			Volume 2 of 25	12/07/98	Merz
	25-78-81		Memantine HCl (Merz/Quintiles) Dementia	Volume 3 of 25	12/07/98	Merz
	25-78-82			Volume 4 of 25	12/07/98	Merz
	25-78-83			Volume 5 of 25	12/07/98	Merz
	25-78-84			Volume 6 of 25	12/07/98	Merz
	25-78-85			Volume 7 of 25	12/07/98	Merz
	25-78-86			Volume 8 of 25	12/07/98	Merz

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Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-87			Volume 9 of 25	12/07/98	Merz
	25-78-88			Volume 10 of 25	12/07/98	Merz
	25-78-89			Volume 11 of 25	12/07/98	Mer[redacted]
	25-78-90			Volume 12 of 25	12/07/98	Merz
	25-78-91			Volume 13 of 25	12/07/98	Merz
	25-78-92			Volume 14 of 25	12/07/98	Merz
	25-78-93			Volume 15 of 25	12/07/98	Merz
	25-78-94			Volume 16 of 25	12/07/98	Merz
	25-78-95			Volume 17 of 25	12/07/98	Merz
	25-78-96		Memantine HCl (Merz/Quintiles) Dementia	Volume 18 of 25	12/07/98	Merz[redacted]
	25-78-97			Volume 19 of 25	12/07/98	Merz
	25-78-98			Volume 20 of 25	12/07/98	Merz
	25-78-99			Volume 21 of 25	12/07/98	Merz
	25-78-100			Volume 22 of 25	12/07/98	Merz
	25-78-101			Volume 23 of 25	12/07/98	Merz

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-102			Volume 24 of 25	12/07/98	Merz
	25-78-103			Volume 25 of 25	12/07/98	Merz
	25-78-104			/032: Protocol Amendment: New Investigator	12/18/98	Mer[redacted]
	25-78-105			/033: IND Safety Report	2/11/98	Merz
	25-78-106		Memantine HCl (Merz/Quintiles) Dementia	/034: Protocol Amendment: Change in Protocol for Protocol #MRZ 90001-9605	2/11/99	Merz
	25-78-107			/035: IND Safety Report	3/09/99	Merz
	25-78-108			/036: IND Safety Report	3/17/99	Mer[redacted]
	25-78-108A			/037: Changes to a Protocol - Request for FDA Response: Protocol MRZ 90001-9605	5/21/99	Quintiles BRI, Inc.
	25-78-108C		Memantine HCl (Merz/Quintiles) Dementia	/039: IND Safety Report	9/22/99	Quintiles BRI, Inc.

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-108D			/040: Other- Response to FDA Letter of 3-Aug-99; Protocol Amendment Submitted on 5/21/99, Regarding Inclusion of a Cognitive Rating Scale in the Primary Outcome Measures Under Consideration	10/13/99	Quintiles BRI, Inc.
	25-78-109			/041: Other: Sub-mission of Final Analysis Plan for Protocol MRZ 90001-9605	12/02/99	Merz
	25-78-110		Memantine HCl (Merz/Quintiles) Dementia	/042: Annual Report 10/9/98 - 10/9/99 Volume 1 of 5	12/08/99	Merz
	25-78-111			Volume 2 of 5	12/08/99	Merz
	25-78-112			Volume 3 of 5	12/08/99	Merz
	25-78-113			Volume 4 of 5	12/08/99	Merz
	25-78-114			Volume 5 of 5	12/08/99	Merz

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-114A			/043: IND Safety Report	1/31/00	Quintiles BRI, Inc.
	25-78-114B			/044: IND Safety Report	3/24/00	Quintiles BRI, I[redacted]
	25-78-115			/045: Transfer of Ownership	9/13/00	Forest
	25-78-116			/046: Request for Pre-NDA (Type B) Meeting	11/09/00	Forest
	25-78-117		Memantine HCl (Merz/Quintiles) Dementia	/047: Annual Report - 10/6/99 - 10/5/00	12/04/00	Forest
	25-78-118			/048: Briefing Book for Pre-NDA (Type B) Meeting	12/26/00	Forest
	25-78-119			/049: Initial IND Safety Report	1/15/01	Forest
	25-78-120			/050: IND Safety Report	1/16/01	Forest
	25-78-121			/051: IND Safety Report	2/13/01	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-122			/052: IND Safety Report	3/02/01	Forest
	25-78-123		Memantine HCl (Merz/Quintiles) Dementia	/053: Minutes of Pre-NDA (Type B) Meeting Held on 1/25/01	3/08/01	Forest
	25-78-124			/054: Request for Special Protocol Assessment - Protocol MEM-MD-01 and MEM-MD-02	3/20/01	Forest
	25-78-125			/055: Response to Questions on the Clinical Pharmacokinetics Program Volume 1 of 7	4/18/01	Forest
	25-78-126			Volume 2 of 7	4/18/01	Forest
	25-78-127			Volume 3 of 7	4/18/01	Forest
	25-78-128			Volume 4 of 7	4/18/01	Forest
	25-78-129			Volume 5 of 7	4/18/01	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-130		Memantine HCl (Merz/Quintiles) Dementia	Volume 6 of 7	4/18/01	Forest
	25-78-131			Volume 7 of 7	4/18/01	Forest
	25-78-132			/056: IND Safety Report	5/21/01	Forest
	25-78-133			/057: Information Amendment: CMC - To Add Forest As A Manufacturer Of Clinical Drug Product	5/21/01	Forest
	25-78-134			/058: Protocol Amendment: New Protocols; MEM-MD-01 and MEM-MD-02	5/21/01	Forest
	25-78-135		Memantine HCl (Merz/Quintiles) Dementia	/059: Protocol Amendment: New Investigator	5/30/01	Forest
	25-78-136			/060: IND Safety Report	6/12/01	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-137			/061: Minutes of 5/16/01 FDA Tele-conference; Held With The Biopharmaceutics Reviewers - Reference To The Protocol Study MEM-PK-01, Divisions Request Letter on 2/15/01	6/19/01	Forest
	25-78-138			/062: Request for Special Protocol Assessment; Clinical Trial-Protocol MEM-MD-10	6/22/01	Forest
	25-78-139		Memantine HCl (Merz/Quintiles) Dementia	/063: Protocol Amendment: New Investigators	7/05/01	Forest
	25-78-140			/064: IND Safety Report	7/10/01	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-141			/065: Protocol Amendment-New Protocol; Protocol Amendment-New Investigator; Study MEM-PK-07	7/17/01	Forest
	25-78-142			/066: Protocol Amendment-New Protocol; Protocol Amendment-New Investigator; Study MEM-PK-01	8/06/01	Forest
	25-78-143		Memantine HCl (Merz/Quintiles) Dementia	/067: Protocol Amendment: New Investigator	8/08/01	Forest
	25-78-144			/068: IND Safety Report	8/16/01	Fore
	25-78-145			/069: IND Safety Report	8/16/01	Forest
	25-78-146			/070: IND Safety Report	8/30/01	Forest
	25-78-147			/071: IND Safety Report	8/30/01	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-148		Memantine HCl (Merz/Quintiles) Dementia	/072: Protocol Amendment: New Protocol; Protocol Amendment: New Investigator-MEM-PK-04	9/10/01	Forest
	25-78-149			/073: Protocol Amendment: New Protocol; MEM-MD-10	9/10/01	Forest
	25-78-150			/074: General Correspondence: Updated Form FDA 1572; Study MEM-PK-07	9/24/01	Forest
	25-78-151			/075: Information Amendment: CMC- Protocol MEM-PK-04	9/28/01	Fore
	25-78-152		Memantine HCl (Merz/Quintiles) Dementia	/076: Protocol Amendment: New Investigator	10/01/01	Forest
	25-78-153			/077: IND Safety Report	10/02/01	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-154			/078: Protocol Amendment: Change In Protocol; Study MEM-PK-04	10/15/01	Forest
	25-78-155			/079: General Correspondence: Updated Form FDA 1572; Study MEM-PK-01	10/16/01	Forest
	25-78-156			/080: General Correspondence: Right of Dr. Dennis Charney to Cross-Reference IND# 33,392	10/18/01	Forest
	25-78-157		Memantine HCl (Merz/Quintiles) Dementia	/081: Protocol Amendment: New Investigators	10/22/01	Forest
	25-78-158			/082: General Correspondence: Pre-NDA Questions	10/26/01	Forest
	25-78-159			/083: IND Safety Report	10/31/01	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-160			/084: IND Safety Report	11/06/01	Forest
	25-78-161			/085: IND Safety Reports	11/12/01	Forest
	25-78-162		Memantine HCl (Merz/Quintiles) Dementia	/086: IND Safety Report	11/14/01	Forest
	25-78-163			/087: IND Follow-Up Safety Report	11/27/01	Forest
	25-78-164			/088: IND and Safety Report	11/30/01	Forest
	25-78-165			/089: Protocol Amendment: New Investigator	11/30/01	Forest
	25-78-166			/090: IND Safety Report	12/04/01	Forest
	25-78-167		Memantine HCl (Merz/Quintiles) Dementia	/091: IND Safety Reports	12/05/01	Forest
	25-78-168			/092: IND Safety Report	12/07/01	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-169			/093: IND Safety Report	12/11/01	Forest
	25-78-170		Memantine HCl (Merz/Quintiles) Dementia	/094: Protocol Amendment: New Protocol; MEM-PK-05	12/17/01	Forest
	25-78-171			/095: IND Safety Report	12/19/01	Forest
	25-78-172			/096: Protocol Amendment: New Investigator	12/21/01	Forest
	25-78-173			/097: IND Safety Report	12/28/01	Forest
	25-78-174			/098: Protocol Amendment: New Investigator	1/07/02	Forest
	25-78-175		Memantine HCl (Merz/Quintiles) Dementia	/099: IND Safety Report	1/09/02	Forest
	25-78-176			/100: Annual Report 10/6/00 - 10/5/01	1/22/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-177			/101: Protocol Amendment: New Investigator	1/23/02	Forest
	25-78-178		Memantine HCl (Merz/Quintiles) Dementia	/102: IND Safety report	1/23/02	Fore[redacted]
	25-78-179			/103: IND Safety Report	2/01/02	Forest
	25-78-180			/104: IND Safety Report	2/01/02	Forest
	25-78-181		Memantine HCl (Merz/Quintiles) Dementia	/105: General Correspondence: On 12/17/01, Serial No. 094 Submitted Protocol MEM-PK-05; This IND Should Have Been Submitted To IND # 52,704; Request To Remove This Protocol From IND# 33,392 And Will Be Appropriately Sub-mitted To IND# 52,704	2/04/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-182			/106: Protocol Amendment: New Investigator	2/08/02	Forest
	25-78-183		Memantine HCl (Merz/Quintiles) Dementia	/107: Protocol Amendment: Change In Protocol; MEM-MD-01 Amendment 1; MEM-MD-02 Amendment 1	2/15/02	Fore[redacted]
	25-78-184			/108: Protocol Amendment: New Investigator	2/25/02	Forest
	25-78-185		Memantine HCl (Merz/Quintiles) Dementia	/109: Letter Of Authorization; For The Division To Refer To the Subject IND In Support Of Clinical Investigations Conducted By Dr. Manji, Who Is Affiliated With The Mood And Anxiety Disorders Program At NIMH	2/26/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-186			/110: 15-Day IND Safety Report	3/05/02	Forest
	25-78-187			/111: 15-Day IND Safety Report	3/15/02	Forest
	25-78-188		Memantine HCl (Merz/Quintiles) Dementia	/112: 15-Day Safety Report	3/18/02	Forest
	25-78-189			/113: 15-Day Safety Report	3/19/02	Forest
	25-78-190		Memantine HCl (Merz/Quintiles) Dementia	/114: 15-Day Safety Report	3/26/02	Forest
	25-78-191			/115: Protocol Amendment: New Protocol MEM-MD-09; New Investigator	3/2802	Forest
	25-78-192			/116: Protocol Amendment: New Investigator	3/2802	Forest
	25-78-193			/117: 15-Day Safety Report	3/29/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-194		Memantine HCl (Merz/Quintiles) Dementia	/118: 15-Day Safety Report	4/01/02	Forest
	25-78-195			/119: 15-Day Safety Report	4/09/02	Forest
	25-78-196			/120: 15-Day Safety Report	4/12/02	Forest
	25-78-197		Memantine HCl (Merz/Quintiles) Dementia	/121: 15-Day Safety Report	4/18/02	Forest
	25-78-198			/122: 15-Day Safety Report	4/25/02	Forest
	25-78-199		Memantine HCl (Merz/Quintiles) Dementia	/123: 15-Day Safety Report	4/25/02	Forest
	25-78-200			/124: 15-Day Safety Report	5/03/02	Forest
	25-78-201		Memantine HCl (Merz/Quintiles) Dementia	/125: 15-Day Safety Report	5/15/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-202		Memantine HCl (Merz/Quintiles) Dementia	/126: 15-Day Safety Report	5/20/02	Forest
	25-78-203		Memantine HCl (Merz/Quintiles) Dementia	/127: 15-Day Safety Report	5/21/02	Fores[redacted]
	25-78-204			/128: Protocol Amendment: New Protocols; Clinical Studies MEM-MD-03, 11, And 12	5/23/02	Forest
	25-78-205		Memantine HCl (Merz/Quintiles) Dementia	/129: 15-Day Safety Report	5/28/02	Forest
	25-78-206		Memantine HCl (Merz/Quintiles) Dementia	/130: 15-Day Safety Report	5/31/02	Fores[redacted]
	25-78-207		Memantine HCl (Merz/Quintiles) Dementia	/131: 15-Day Safety Report	6/04/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-208		Memantine HCl (Merz/Quintiles) Dementia	/132: Protocol Amendment: New Investigators For Protocol MEM-MD-11	6/06/02	Forest
	25-78-209		Memantine HCl (Merz/Quintiles) Dementia	/133: 15-Day Safety Report	6/07/02	Forest
	25-78-210		Memantine HCl (Merz/Quintiles) Dementia	/134: Protocol Amendment: New Investigator Volumes 1 of 2	6/10/02	Forest
	25-78-211			Volume 2 of 2	6/10/02	Forest
	25-78-212		Memantine HCl (Merz/Quintiles) Dementia	/135: 15-Day Safety Report	6/13/02	Forest
	25-78-213		Memantine HCl (Merz/Quintiles) Dementia	/136: General Corre-spondence: Request From The Division Document Entitled, "Assessment Of Abuse Potential-Memantine", Dated 6/5/02 And References	6/14/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-214			/137: 15-Day Safety Report	7/3/02	Forest
	25-78-215			/138: 15-Day Safety Report	7/11/02	Fores[redacted]
	25-78-216		Memantine HCl (Merz/Quintiles) Dementia	/139: Protocol Amendment: New Protocol/New Investigator: MEM-PK-02	7/11/02	Forest
	25-78-217			/140: 15-Day Safety Report	7/22/02	Forest
	25-78-218			/141: 15-Day Safety Report	7/24/02	Forest
	25-78-219		Memantine HCl (Merz/Quintiles) Dementia	/142: 15-Day Safety Report	7/26/02	Fore[redacted]
	25-78-220			/143: Information Amendment-Clinical: Statistical Analysis Plan For Protocol MEM-MD-02	7/29/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-221		Memantine HCl (Merz/Quintiles) Dementia	/144: 15-Day IND Safety Report	7/30/02	Forest
	25-78-222		Memantine HCl (Merz/Quintiles) Dementia	/145: 15-Day IND Safety Report	8/05/02	Fore
	25-78-223			/146: 15-Day IND Safety Report	8/07/02	Forest
	25-78-224		Memantine HCl (Merz/Quintiles) Dementia	/147: 15-Day IND Safety Report	8/07/02	Forest
	25-78-225			/148: Protocol Amendment: New Investigator	8/13/02	Forest
	25-78-226			/149: 15-Day IND Safety Report	8/14/02	Forest
	25-78-227		Memantine HCl (Merz/Quintiles) Dementia	/150: 15-Day IND Safety Report	8/19/02	Forest
	25-78-228			/151: 15-Day IND Safety Report	8/23/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-229			/152: Protocol Amendment: Change In Protocol MEM-MD-02 Amendment 2; Infor-mation Amendment-Clinical (SAP Amendment 1 To Protocol MEM-MD-02)	8/29/02	Forest
	25-78-230		Memantine HCl (Merz/Quintiles) Dementia	/153: 15-Day IND Safety Report	9/03/02	Forest
	25-78-231			/154: 15-Day IND Safety Report	9/05/02	Forest
	25-78-232		Memantine HCl (Merz/Quintiles) Dementia	/155: 15-Day IND Safety Report	9/06/02	Forest
	25-78-233			/156: Protocol Amendment: Change In Protocol (Protocol MEM-PK-02 Amendment A)	9/11/02	Forest
	25-78-234		Memantine HCl (Merz/Quintiles) Dementia	/157: 15-Day IND Safety Report	9/11/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-235		Memantine HCl (Merz/Quintiles) Dementia	/158: 15-Day IND Safety Report	9/17/02	Forest
	25-78-236		Memantine HCl (Merz/Quintiles) Dementia	/159: Protocol Amendment: New Protocol/New Investigator (MEM-MD-17)	9/20/02	Fore[redacted]
	25-78-237			/160: Protocol Amendment: New Investigator	9/23/02	Forest
	25-78-238		Memantine HCl (Merz/Quintiles) Dementia	/161: 15-Day IND Safety Report	9/24/02	Forest
	25-78-239			/162: 15-Day IND Safety Reports	9/26/02	Fore[redacted]
	25-78-240		Memantine HCl (Merz/Quintiles) Dementia	/163: 15-Day IND Safety Report	10/3/02	Forest
	25-78-241			/164: 15-Day IND Safety Report	10/4/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-242		Memantine HCl (Merz/Quintiles) Dementia	/165: 15-Day IND Safety Report	10/11/02	Forest
	25-78-243			/166: 15-Day IND Safety Report	10/11/02	Fore[redacted]
	25-78-244		Memantine HCl (Merz/Quintiles) Dementia	/167: Protocol Amendment-Change In Protocol (MEM-MD-03 Amendments 1 And 2)	10/14/02	Forest
	25-78-245			/168: 15-Day IND Safety Report	10/15/02	Forest
	25-78-246		Memantine HCl (Merz/Quintiles) Dementia	/169: 15-Day IND Safety Report	10/17/02	Forest
	25-78-247			/170: General Correspondence; Proposal For the Resubmission Of NDA 21-487 Based Upon FDA Comments Regarding Format Of NDA	10/18/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-248		Memantine HCl (Merz/Quintiles) Dementia	/171: 15-Day IND Safety Report	10/18/02	Forest
	25-78-249			/172: 15-Day IND Safety	10/22/02	Fores[redacted]
	25-78-250		Memantine HCl (Merz/Quintiles) Dementia	/173: 15-Day IND Safety Report	10/24/02	Forest
	25-78-251			/174: 15-Day IND Safety Report	11/01/02	Forest
	25-78-252		Memantine HCl (Merz/Quintiles) Dementia	/175: 15-Day IND Safety Report	11/04/02	Forest
	25-78-253			/176: 15-Day IND Safety Report	11/05/02	Fores[redacted]
	25-78-254		Memantine HCl (Merz/Quintiles) Dementia	/177: 15-Day IND Safety Report	11/11/02	Forest
	25-78-255			/178: 15-Day IND Safety Report	11/12/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-256		Memantine HCl (Merz/Quintiles) Dementia	/179: 15-Day IND Safety Report	11/12/02	Forest
	25-78-257			/180: 15-Day IND Safety Report	11/13/02	Fores
	25-78-258		Memantine HCl (Merz/Quintiles) Dementia	/181: 15-Day IND Safety Report	11/20/02	Forest
	25-78-259			/182: 15-Day IND Safety Report	11/21/02	Forest
	25-78-260			/183: Information Amendment: Request For Waiver Of IND Annual Report (Reporting Period 10/6/01 TO 10/5/02)	11/22/02	Forest
	25-78-261		Memantine HCl (Merz/Quintiles) Dementia	/184: 15-Day IND Safety Report	11/25/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-262			/185: General Correspondence: Request For Review (Proposal For Collection Of Epidemiological Data To assess Abuse Liability)	11/27/02	Forest
	25-78-263		Memantine HCl (Merz/Quintiles) Dementia	/186: 15-Day IND Safety Report	11/27/02	Forest
	25-78-264			/187: 15-Day IND Safety Report	12/2/02	Forest
	25-78-265		Memantine HCl (Merz/Quintiles) Dementia	/188: 15-Day IND Safety Report	12/3/02	Forest
	25-78-266			/189: 15-Day IND Safety Report	12/6/02	Forest
	25-78-267			/190: Protocol Amendment-New Investigator	12/9/02	Forest
	25-78-268		Memantine HCl (Merz/Quintiles) Dementia	/191: 15-Day IND Safety Report	12/13/02	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-269			/192: 15-Day IND Safety Report Initial	12/20/02	Forest
	25-78-270		Memantine HCl (Merz/Quintiles) Dementia	/193: 15-Day IND Safety Report	12/23/02	Forest
	25-78-271			/194: Protocol Amendment: Change In Protocol (MEM-MD-01 Amendment 2; MEM-MD-11 Amendment 1)	12/26/02	Forest
	25-78-272			/195: 15-Day IND Safety Report	12/27/02	Forest
	25-78-273		Memantine HCl (Merz/Quintiles) Dementia	/196: 15-Day IND Safety Report	1/2/03	Forest
	25-78-274			/197: 15-Day IND Safety Report	1/7/03	Forest
	25-78-275		Memantine HCl (Merz/Quintiles) Dementia	/198: 15-Day IND Safety Report	1/9/03	Forest
	25-78-276			/199: 15-Day IND Safety Report	1/10/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-277			/200: General Correspondence: Request For Review (Sub-mission Of Potential Brand Names)	1/13/03	Forest
	25-78-278		Memantine HCl (Merz/Quintiles) Dementia	/201: 15-Day IND Safety Report	1/14/03	Forest
	25-78-279			/202: Protocol Amendment-Change In Protocol (MEM-MD-12 Amendment 1)	1/15/03	Forest
	25-78-280			/203: 15-Day Alert Report	1/17/03	Forest
	25-78-281		Memantine HCl (Merz/Quintiles) Dementia	/204: General Correspondence: Request For Review (Proposal For Collection Of Epidemiological Data To Assess Abuse Liability	1/20/03	Forest
	25-78-282			/205: 15-Day IND Safety Report	1/21/03	Forest
	25-78-283			/206: 15-Day IND Safety Report	1/23/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-284		Memantine HCl (Merz/Quintiles) Dementia	/207: 15-Day IND Safety Report	1/24/03	Forest
	25-78-285			/208: 15-Day IND Safety Report	1/28/03	Fore[redacted]
	25-78-286		Memantine HCl (Merz/Quintiles) Dementia	/209: 15-Day IND Safety Report	2/4/03	Forest
	25-78-287			/210: Information Amendment: Clinical (SAP For Protocol MEM-MD-12) Request For Review And Feedback	2/4/03	Forest
	25-78-288		Memantine HCl (Merz/Quintiles) Dementia	/211: 15-Day IND Safety Report	2/7/03	Forest
	25-78-289			/212: 15-Day IND Safety Report	2/7/03	Fore[redacted]
	25-78-290		Memantine HCl (Merz/Quintiles) Dementia	/213: 15-Day IND Safety Report	2/12/03	Forest
	25-78-291			/214: Response To Request For Information (Biometrics Comment On Protocol MEM-MD-02 and SAP)	2/13/03	Forest

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-292			/215: 15-Day IND Safety Report	2/19/03	Forest
	25-78-293		Memantine HCl (Merz/Quintiles) Dementia	/216: Protocol Amendment: Change In Protocol (MEM-MD-17 Amendment 1)	2/25/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-294			/217: 15-Day IND Safety Report	2/27/03	Forest
	25-78-295			/218: 15-Day IND Safety Report	2/28/03	Forest
	25-78-296		Memantine HCl (Merz/Quintiles) Dementia	/219: 15-Day IND Safety Report	3/3/03	Fore[redacted]
	25-78-297			/220: 15-Day IND Safety Report	3/10/03	Forest
	25-78-298			/221: Protocol Amendment: New Investigator	3/11/03	Forest
	25-78-299		Memantine HCl (Merz/Quintiles) Dementia	/222: 15-Day IND Safety Report	3/12/03	Forest
	25-78-300			/223: 15-Day IND Safety Report	3/14/03	Forest
	25-78-301		Memantine HCl (Merz/Quintiles) Dementia	/224: General Correspondence: Response To FDA Comments On Statistical Analysis Plan (SAP) For Protocol MEM-MD-12; Request For Teleconference	3/14/03	Fores[redacted]
	25-78-302			/225: 15-Day IND Safety Report	3/17/03	Forest

SUBMISSIONS LOG

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-303		Memantine HCl (Merz/Quintiles) Dementia	/226: 15-Day IND Safety Report	3/19/03	Forest
	25-78-304			/227: 15-Day IND Safety Report	3/20/03	Fores
	25-78-305			/228: Protocol Amendment: Change In Protocol (MEM-MD-10 Amendments 1 & 2; MEM-MD-11 Amendment 2)	3/24/03	Forest
	25-78-306		Memantine HCl (Merz/Quintiles) Dementia	/229: 15-Day IND Safety Report	3/24/03	Forest
	25-78-307			/230: 15-Day IND Safety Report	3/26/03	Forest
	25-78-308		Memantine HCl (Merz/Quintiles) Dementia	/231: 15-Day IND Safety Report	4/2/03	Fores
	25-78-309			/232: 15-Day IND Safety Report	4/7/03	Forest
	25-78-310		Memantine HCl (Merz/Quintiles) Dementia	/233: 15-Day IND Safety Report	4/8/03	Forest
	25-78-311			/234: 15-Day IND Safety Report	4/9/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-312			/235: 15-Day IND Safety Report	4/10/03	Forest
	25-78-313		Memantine HCl (Merz/Quintiles) Dementia	/236: 15-Day IND Safety Report	4/11/03	Forest
	25-78-314			/237: 15-Day IND Safety Report	4/14/03	Forest
	25-78-315		Memantine HCl (Merz/Quintiles) Dementia	/238: 15-Day IND Safety Report	4/15/03	Forest
	25-78-316			/239: 15-Day IND Safety Report	4/17/03	Forest
	25-78-317		Memantine HCl (Merz/Quintiles) Dementia	/240: 15-Day IND Safety Report	4/18/03	Forest
	25-78-318			/241: 15-Day IND Safety Report	4/21/03	Forest
	25-78-319		Memantine HCl (Merz/Quintiles) Dementia	/242: 15-Day IND Safety Report	4/23/03	Forest
	25-78-320			/243: 15-Day IND Safety Report	4/24/03	Forest
	25-78-321		Memantine HCl (Merz/Quintiles) Dementia	/244: 15-Day IND Safety Report	4/25/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-322			/245: 15-Day IND Safety Report	4/28/03	Forest
	25-78-323		Memantine HCl (Merz/Quintiles) Dementia	/246: 15-Day IND Safety Report	5/1/03	Forest
	25-78-324			/247: 15-Day IND Safety Report	5/6/03	Forest
	25-78-325		Memantine HCl (Merz/Quintiles) Dementia	/248: 15-Day IND Safety Report	5/7/03	Forest
	25-78-326			/249: 15-Day IND Safety Report	5/7/03	Forest
	25-78-327		Memantine HCl (Merz/Quintiles) Dementia	/250: 15-Day IND Safety Report	5/9/03	Forest
	25-78-328			/251: 15-Day IND Safety Report	5/14/03	Forest
	25-78-329		Memantine HCl (Merz/Quintiles) Dementia	/252: 15-Day IND Safety Report	5/19/03	Forest
	25-78-330			/253: 15-Day IND Safety Report	5/22/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-331		Memantine HCl (Merz/Quintiles) Dementia	/254: 15-Day IND Safety Report	5/23/03	Forest
	25-78-332			/255: 15-Day IND Safety Report	5/27/03	Forest
	25-78-333		Memantine HCl (Merz/Quintiles) Dementia	/256: 15-Day IND Safety Report	5/28/03	Forest
	25-78-334			/257: Information Amendment-Clinical (SAP Amendment 1 For Protocol MEM-MD-12)	5/28/03	Forest
	25-78-335			/258: 15-Day IND Safety Report	5/29/03	Forest
	25-78-336		Memantine HCl (Merz/Quintiles) Dementia	/259: 15-Day IND Safety Report	6/2/03	Forest

SUBMISSIONS LOG

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-337			/260: Information Amendment-Clinical (Investigator Brochure, Version 3, Dated 5/15/03)	6/2/03	Forest
	25-78-338			/261: 15-Day IND Safety Report	6/3/03	Forest
	25-78-339		Memantine HCl (Merz/Quintiles) Dementia	/262: 15-Day IND Safety Report	6/4/03	Forest
	25-78-340			/263: 15-Day IND	6/6/03	Forest
	25-78-341		Memantine HCl (Merz/Quintiles) Dementia	/264: 15-Day IND Safety Report	6/9/03	Forest
	25-78-342			/265: 15-Day IND Safety Report	6/10/03	Forest
	25-78-343			/266: Protocol Amendment-Change In Protocol(MEM-MD-03 Amendment 3)	6/11/03	Forest
	25-78-344		Memantine HCl (Merz/Quintiles) Dementia	/267: 15-Day IND Safety Report	6/12/03	Forest
	25-78-345			/268: 15-Day IND Safety Report	6/16/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-346		Memantine HCl (Merz/Quintiles) Dementia	/269: 15-Day IND Safety Report	6/17/03	Forest
	25-78-347			/270: 15-Day IND Safety Report	6/18/03	Fore[redacted]
	25-78-348		Memantine HCl (Merz/Quintiles) Dementia	/271: 15-Day IND Safety Report	6/19/03	Forest
	25-78-349			/272: 15-Day IND Safety Report	6/19/03	Forest
	25-78-350		Memantine HCl (Merz/Quintiles) Dementia	/273: 15-Day IND Safety Report	6/23/03	Forest
	25-78-351			/274: 15-Day IND Safety Report	6/24/03	Forest
	25-78-352			/275: Protocol Amendment-New Investigator (MEM-MD-03)	6/24/03	Fores[redacted]
	25-78-353		Memantine HCl (Merz/Quintiles) Dementia	/276: 15-Day IND Safety Report	6/25/03	Forest
	25-78-354			/277: 15-Day IND Safety Report	7/1/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-355		Memantine HCl (Merz/Quintiles) Dementia	/278: 15-Day IND Safety Report	7/3/03	Forest
	25-78-356			/279: 15-Day IND Safety Report	7/8/03	Fores
	25-78-357		Memantine HCl (Merz/Quintiles) Dementia	/280: 15-Day IND Safety Report	7/9/03	Forest
	25-78-358			/281: 15-Day IND Safety Report	7/10/03	Forest
	25-78-359		Memantine HCl (Merz/Quintiles) Dementia	/282: 15-Day IND Safety Report	7/14/03	Forest
	25-78-360			/283: 15-Day IND Safety Report	7/15/03	Forest
	25-78-361		Memantine HCl (Merz/Quintiles) Dementia	/284: 15-Day IND Safety Report	7/16/03	Forest
	25-78-362			/285: 15-Day IND Safety Report	7/17/03	Forest
	25-78-363		Memantine HCl (Merz/Quintiles) Dementia	/286: 15-Day IND Safety Report	7/18/03	Forest
	25-78-364			/287: 15-Day IND Safety Report	7/21/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-365		Memantine HCl (Merz/Quintiles) Dementia	/288: 15-Day IND Safety Report	7/22/03	Forest
	25-78-366			/289: 15-Day IND Safety Report	7/23/03	Fore[redacted]
	25-78-367		Memantine HCl (Merz/Quintiles) Dementia	/290: 15-Day IND Safety Report	7/24/03	Forest
	25-78-368			/291: 15-Day IND Safety Report	7/25/03	Forest
	25-78-369		Memantine HCl (Merz/Quintiles) Dementia	/292: 15-Day IND Safety Report	7/28/03	Forest
	25-78-370			/293: 15-Day IND Safety Report	7/29/03	Forest
	25-78-371		Memantine HCl (Merz/Quintiles) Dementia	/294: 15-Day IND Safety Report	7/30/03	Fores[redacted]
	25-78-372			/295: 15-Day IND Safety Report	8/1/03	Forest
	25-78-373			/296 15-Day IND Safety Report	8/403	Forest
	25-78-374		Memantine HCl (Merz/Quintiles) Dementia	/297 15-Day IND Safety Report	8/6/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-375			/298: 15-Day IND Safety Report	8/7/03	Forest
	25-78-376		Memantine HCl (Merz/Quintiles) Dementia	/299: 15-Day IND Safety Report	8/11/03	Forest
	25-78-377			/300: 15-Day IND Safety Report	8/13/03	Forest
	25-78-378		Memantine HCl (Merz/Quintiles) Dementia	/301: 15-Day IND Safety Report	8/14/03	Forest
	25-78-379			/302: 15-Day IND Safety Report	8/18/03	Forest
	25-78-380			/303: Protocol Amendment-Change In Protocol (MEM-MD-12 Amendment 2)	8/18/03	Forest
	25-78-381		Memantine HCl (Merz/Quintiles) Dementia	/304: 15-Day IND Safety Report	8/19/03	Forest
	25-78-382			/305: 15-Day IND Safety Report	8/21/03	Forest
	25-78-383			/306: 15-Day IND Safety Report	8/22/03	Forest
	25-78-384		Memantine HCl (Merz/Quintiles) Dementia	/307: 15-Day IND Safety Report	8/26/03	Forest

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AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-385			/308: 15-Day IND Safety Report	8/27/03	Forest
	25-78-386			/309: 15-Day IND Safety Report	8/28/03	Forest
	25-78-387		Memantine HCl (Merz/Quintiles) Dementia	/310: 15-Day IND Safety Report	9/5/03	Fores
	25-78-388			/311: 15-Day IND Safety Report	9/8/03	Forest
	25-78-389			/312: 15-Day IND Safety Report	9/10/03	Forest
	25-78-390		Memantine HCl (Merz/Quintiles) Dementia	/313: Information Amendment-Clinical (SAP For Protocol MEM-MD-10)	9/15/03	Forest
	25-78-391			/314: 15-Day IND Safety Report; General Correspondence-Inadvertent Resubmission Of 15-Day IND Safety Report (T03-USA-03288-01);	9/15/03	Forest
	25-78-392			/315: 15-Day IND Safety Report	9/17/03	Forest
	25-78-393		Memantine HCl (Merz/Quintiles) Dementia	/316: 15-Day IND Safety Report	9/22/03	Forest

SUBMISSIONS LOG

Revised: 11/04/03

AGENCY #	HARD COPY #	MICRO-FILM #	PRODUCT NAME	DESCRIPTION	DATE	COMPANY
IND# 33,392	25-78-394			/317: 15-Day IND Safety Report	9/23/03	Forest
	25-78-395			/318: 15-Day IND Safety Report	9/26/03	Forest
	25-78-396		Memantine HCl (Merz/Quintiles) Dementia	/319: Protocol Amendment-Change In Protocol (MEM-MD-17 Amendment 2); Protocol Amendment-New Investigator	9/26/03	Fores
	25-78-397			/320: 15-Day IND Safety Report	9/30/03	Forest
	25-78-398			/321: 15-Day IND Safety Report	10/7/03	Forest
	25-78-399		Memantine HCl (Merz/Quintiles) Dementia	/322: 15-Day IND Safety Report	10/9/03	Forest

FAX: 201-524-9711
DIRECT LINE: 201-386-2123

September 13, 2000

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Center for Drug Evaluation and Research
Attn: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Re: **IND 33,392/SN 045: Transfer of IND Sponsorship**
Product: **Memantine HCl**

Dear Dr. Katz:

Enclosed please find a copy of a letter from Merz + Co. GmbH & Co. transferring sponsorship of IND 33,392 (Memantine HCl) to Forest Laboratories, Inc. Henceforth Forest assumes all responsiblites for this IND.

Please call me at 201-386-2123 if you have any questions regarding this material.

Sincerely,

Lester S. Gibbs, PhD
Manager, Regulatory Affairs

FOREST LABORATORIES, INC.
PLAZA THREE, SUITE 602

HARBORSIDE FINANCIAL CENTER
NEW JERSEY, NJ 07311

Merz+Co.

MERZ

Merz+Co. GmbH & Co. · Postfach 11 13 53 · 60048 Frankfurt am Main

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Document Control Room 4008
5600 Fishers Lane

Rockville, MD 20857

Eckenheimer Landstr. 100-104
60318 Frankfurt am Main
Telefon 0 69/1 50 31
Telex 4 14 031 merz ffm
Telefax 0 69/5 96 21 50
Telegramm-Adresse:
Merzco Frankfurtmain
http://www.merz.de

Ihre Nachricht	Ihr Zeichen	Unser Zeichen	Fernsprechdurchwahl	Datum
		Zim	15 03 -386	September 05th, 2000

Re: IND 33,392- memantine hydrochloride
Transfer of Sponsorship
Serial No.:

Dear Dr. Katz:

Merz + Co. GmbH & Co. hereby transfers sponsorship of the subject IND to Forest Laboratories, Harborside Financial Center, Plaza Three Suite 602, Jersey City, NJ 07311. This transfer is effective from now on.

A letter from Forest acknowledging the transfer and accepting the obligations of the sponsor with respect to this IND is submitted concurrently with this notification.

Sincerely yours,
Merz + Co. GmbH & Co.

(Prof. Hans Erbler)
President Pharma Division

(Dr. Matthias Zimmermann)
Head of Drug Regulatory Affairs

FAX: 201-524-9711
DIRECT LINE: 201-386-2131

December 19, 2002

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Center for Drug Evaluation and Research
Attn: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-487/Memantine HCl
Original New Drug Application

Dear Dr. Katz:

Forest Laboratories, Inc. hereby submits, in duplicate, an original New Drug Application for memantine hydrochloride tablets, 5mg, 10 mg, 15 mg and 20 mg, pursuant to the requirements of section 505 (b)(1) of the Federal, Food, Drug and Cosmetic Act, 21 CFR 314.50 and supporting Food and Drug Administration guidelines.

Memantine tablets are intended for the treatment of moderate to severe dementia of the Alzheimer's type. As of November 30, 2002, memantine hydrochloride has received marketing authorization in 41 countries. It is marketed under the tradename Akatinol® in 23 countries mainly for the treatment of mild to moderate dementia syndrome. On May 21, 2002 Merz Pharmaceuticals received registration for memantine by the European Commission for the treatment of moderately severe to severe Alzheimer's Disease under the tradename Axura®. Memantine is also marketed under the tradename Ebixa® by Lundbeck.

Clinical safety data in this NDA, derived from 53 completed trials with memantine, are included in this submission. Twenty-six of these trials were conducted in patients with dementia or other neurological conditions. The remaining 27 trials are clinical pharmacology studies. For purposes of the safety analyses, the completed clinical trials with memantine have been organized into the following groups: Group 1 includes seven placebo-controlled studies in dementia, four open-label extensions of these studies and 2 placebo-controlled studies in neuropathic pain, in which all adverse events were reported regardless of causality; Group 2 includes thirteen studies in which only adverse events considered to be drug related were reported; Group 3A includes 8 clinical pharmacology studies in healthy subjects, for which electronic safety data are available; Group 3B includes 19 clinical pharmacology studies for which limited safety data are available. These studies are summarized and discussed separately in the ISS.

A total of 2302 patients and healthy subjects received memantine in the completed Group 1, Group 2 and Group 3A studies. A total of 1546 patients were included in the Group 1 studies (double-blind and open label). An additional 210 subjects received memantine in Group 3B studies, and more than 3600 patients received memantine in other investigations (e.g. post-marketing studies, drug experience reports) for which limited safety information is available. A total of 21 studies with memantine were ongoing as of April 30, 2002 (the clinical cut-off date for this submission). These include ten studies in dementia, five studies in other indications, two bioavailability/bioequivalence studies, one non-US post-marketing study and three drug-drug interaction studies. Fifteen of these studies were being conducted in the United States. Across all 21 ongoing studies, an estimated total of 2625 patients/subjects had received memantine as of April 30, 2002.

The final report for Study MEM-MD-02, entitled, "Randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of memantine in patients with moderate to severe dementia of the Alzheimer's type," will be submitted during the 60 day review period. Information from the following ongoing pharmacokinetic studies will be made available as completed study reports at the 120-Day Update submission: 1) a bioequivalence trial between tablets manufactured by Forest and Merz and food effects for the Forest formulation (Study MEM-PK-01), 2) an interaction study with memantine and donepezil (Study MEM-PK-07), and 3) a comparative bioavailability study of IR and MR formulation (Study MEM-PK-04).

The Chemistry Manufacturing and Controls Section contains information on the drug product manufactured in Ireland (Forest Laboratories Ireland Ltd.) and drug substance manufactured in Germany (Merz and Company). As requested, a field copy of the Chemistry, Manufacturing and Controls Section (Section 4), Application Summary (Section 3), and the Application Form (356h) and Certification Statement is being submitted to the New York district office.

The Pharmacology/Toxicology Section of the NDA includes studies evaluating nonclinical safety and pharmacology of memantine. A comprehensive program of preclinical studies was conducted with memantine. These trials included acute, subchronic and chronic (both by dietary and gavage dosing), carcinogenicity, reproduction, developmental and genetic toxicity and ADME studies. Additional, specialized studies to investigate the potential for memantine to induce ocular toxicity and Olney-type lesions were carried out.

The Human Pharmacokinetics and Bioavailability Section of the NDA contains reports for all completed clinical pharmacokinetic studies. A total of 20 studies are included in this section. The studies include bioavailability and bioequivalence, pharmacokinetics in normal subjects, Alzheimer's patients, special population, drug-drug interaction studies and drug-food interaction studies.

The NDA contains 437 hardcopy volumes. Each volume is paginated separately. *Item 4* (Chemistry), *Item 5* (Pharmacology and Toxicology), *Item 6* (Human Pharmacokinetics and Bioavailability), *Item 8* (Clinical), and *Item 10* (Statistical) are preceded by copies of *Items 1, 2, and 3* (Table of Contents, Labeling and Application Summary). Based upon Forest's NDA format proposal submitted to the Division on October 18, 2002, and an electronic sample of case report forms submitted on November 12, 2002, the Division and Forest reached agreement on the

outstanding items regarding the format of the NDA. *Items 2, 8/10, 11 and 12* of the NDA are provided electronically, for both the archive and review copies of the submission in accordance with the *January 1999 Guidance for Industry: Providing Regulatory Submission in Electronic Format-NDAs. Item 2* (Labeling) is provided in PDF and MS Word version of the Draft Package Insert. *Items 8/10* (Clinical/Statistical Data) includes PDF versions of the after-text tables/listings for pivotal studies MRZ 9605, MRZ 9403 and after-text tables for the ISE and ISS. *Item 11* (Case Report Tabulations) is provided as SAS Transport datasets for studies designated in Groups 1 and 3A (Group 3A study data are pooled into the datasets corresponding to the integrated summary of safety). *Item 12* (Case Report Forms) is provided as PDF files for patients in Group 1 and 3A studies who experienced serious adverse events, died and/or withdrew from the study due to an adverse experience. Pursuant to discussions with the agency concerning the handling of foreign-language casebooks, Forest has provided full translations of every executed foreign CRF page in addition to the native-language pages. Pages and comments were left in the casebooks untranslated *only* if the pages were crossed-out or voided. The files are provided on Type 3 DLT 10/20 GB format digital tape using NT server 4.0. This tape contains about 9 GB of data. McAfee Virus scan version 4.5.1 was used to ensure the material on CDROMs is virus-free.

Forest believes that the indication being proposed (treatment of moderate to severe dementia of the Alzheimer's type) meets the criteria for priority review, since no satisfactory alternative therapies exist for patients suffering with Alzheimer's Disease of this severity.

In accordance with the Federal Register notice of August 2, 2002, a check in the amount of $533,400.00 was submitted on November 12, 2002 as the user fee payment for a human drug application with clinical data.

If you have any questions at any time during the review process regarding the material submitted, forest representatives would be pleased to discuss them with you. Please contact me at (201) 386-2131 by phone or facsimile at 201-524-9711 if you have any questions regarding the submitted material.

Sincerely,

Doreen V. Morgan

Doreen V. Morgan, Pharm.D., M.S.
Director, Regulatory Affairs

Enc: Type 3 DLT 10/20 GB digital tape of the electronic components of the enclosed NDA